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VOLUME 9
1930

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

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ARCHIVES OF PATHOLOGY

VOLUME 9

JANUARY, 1930—IN TWO PARTS—PART I

NUMBER 1

IMMUNOLOGIC ASPECTS OF THE SEXUAL CYCLE

I. ANAPHYLACTIC STUDIES WITH MAMMALIAN
TOLLUICULAR FLUID¹

W. R. LYONS, B.A.

AND

I. RENI VAN DE CARR, B.A.

The interest in the problems of endocrinology and sex physiology during the last decade has resulted in establishing the importance of autacoid substances as body regulators. During this time the analysis of these problems has been almost entirely from a physiologic standpoint rather than from an immunologic one, owing, no doubt to the fact that the old theory of immunity and species-specificity rather precluded the application of these principles to problems of sex physiology. Gradually, however, new concepts of immunity have been formed which modify somewhat the older theories.

Hektoen¹ in 1927 brought attention to certain of these newer concepts. He said:

It is of special interest that in connection with fundamental problems of immune specificity and the production of antibodies these nonspecies-specific antigens can evoke the formation of corresponding antibodies in the homologous species at least under certain conditions. In view of this circumstance may it not be well to subject to renewed scrutiny the old assumption that species-specific antigens are incapable of provoking any antibody response in their own species?

The early work of Wells,² Dale and Hartley,³ and Dale and Dakin⁴ distinguishing the various ovoproteins and at the same time demon-

¹ Submitted for publication Oct. 4, 1929.

² From the Department of Anatomy and the G. W. Hooper Foundation for Medical Research, University of California.

³ Aided by grants from Eli Lilly and Company and the Committee for Research in Problems of Sex of the National Research Council.

¹ Hektoen, L. Observations with the Precipitin Reaction, *J. Immunol.* **14** 1, 1927.

² Wells, H. G. Studies on the Chemistry of Anaphylaxis (III), *J. Infect. Dis.* **9** 147, 1911.

³ Dale, H. H., and Hartley, P. Anaphylaxis to the Separated Proteins of Horse Serum (Note on Anaphylaxis to Pure Egg Albumin), *Biochem. J.* **10** 408, 1916.

⁴ Dale, H. H., and Dakin, H. D. Chemical Structure and Antigentic Specificity. A Comparison of the Crystalline Egg Albumin of the Hen and the Duck, *Biochem. J.* **13** 248, 1919.

stating the chemical relationships of the ovoproteins of various species of birds, directed our efforts to what might be considered similar study in the mammal, namely, the immunologic relationship of mammalian follicular fluids

It is felt that the data here presented lend support to a theory that graafian follicular fluid, the product of granulosa epithelium and probably of the ovum of the guinea-pig, is relatively nonspecies-specific and auto-antigenic and that the formation of antibodies against it may be responsible for certain cyclic conditions attending that animal in sixteen or seventeen day cycles

It has been our hope that these conditions in the female guinea-pig may serve in a study of the histologic and physiologic aspects of immunity, a problem suggested to us by Dr Herbert M Evans and Dr Karl F Meyer

The first part of the experimental work here reported deals entirely with the immunologic relations of mammalian follicular fluids, and because of the ease in carrying out gross anaphylactic reactions only these reactions were used at this time. We have however, been interested in studying the sex cycle of the female guinea-pig and in understanding its various stages from an immunologic point of view based on what seems to be an extremely sensitive balance of graafian follicular fluid and antistances. Therefore, in the second part of this work, we have continued a study of the gross anaphylactic reactions representing them graphically by means of the bronchospasm reaction, and have included correlative histologic studies of the ovaries. The Schultz-Dale smooth muscle reaction has lent itself especially well to our purpose and in the third part, representative charts obtained with this method are reproduced together with the histologic studies. It may be mentioned that this phase of the study is not complete.

GROSS SHOCK AS CRITERION OF HYPERSENSITIVITY

The work reported in this section has to do with the demonstration of (1) the antigenicity of follicular fluid (2) the antigenic relationship of various follicular fluids and (3) the auto-antigenicity of follicular fluid. Ten healthy guinea-pigs (seven females and three males), weighing from 450 to 500 Gm. were sensitized by the intraperitoneal injection into each of 0.5 cc. of sow's follicular fluid two or three weeks previous to experimentation. The estrous cycles of the female animals had been observed over a three months' period. The animals were given the critical dose of 0.5 cc. each of sow's follicular fluid intracardially (fourteen days after the last estrus of the females). All the animals went through the classic syndrome of anaphylaxis terminating in death.

Next, five normal male guinea-pigs, weighing 500 Gm. each, were sensitized with 0.5 cc. each of sow's follicular fluid by intraperitoneal

injection At the end of two weeks each of these animals received an intracardial injection of 0.5 cc of cow's follicular fluid All the animals gave the typical symptoms of anaphylactic shock terminating in death

To demonstrate the antigenic relationship of mare's follicular fluid to sow's follicular fluid, two normal female guinea-pigs, weighing from 400 to 450 Gm were sensitized with 0.5 cc each, of sow's follicular fluid, given intraperitoneally The critical dose of mare's follicular fluid was given intracardially three weeks after sensitization Both animals went through severe anaphylactic shock, but eventually recovered Two normal male guinea-pigs sensitized with 1.5 cc, each, of sow's follicular fluid each received an intracardial injection of 3 cc of mare's follicular fluid twenty-one days later Both died with typical anaphylactic symptoms

To show a similar relationship when the animals were sensitized to one of the other follicular fluids, twelve normal guinea-pigs (each weighing about 500 Gm) were sensitized with 0.5 cc, each, of cow's follicular fluid, given intraperitoneally Three weeks later, five of these animals died with typical symptoms of anaphylactic shock following the injection of 0.5 cc, each, of cow's follicular fluid intracardially Another five died from anaphylactic shock after the intracardial injection of 0.5 cc, each, of sow's follicular fluid Of the remaining animals, one was given 0.5 cc of mare's follicular fluid and another 0.5 cc of sheep's follicular fluid intracardially The latter died with the classic symptoms of anaphylaxis within five minutes, the first animal, receiving mare's follicular fluid, suffered severe anaphylaxis but recovered Five normal male guinea-pigs were then sensitized with 2 cc, each, of cow's follicular fluid, given intraperitoneally Three weeks later four of these animals suffered severe shock, but recovered after the intracardial injection of 2 cc, each of mare's follicular fluid, while the remaining one died with typical symptoms following injection of 3 cc of mare's follicular fluid

In order to show that the female guinea-pig is auto-immunized to follicular protein and desensitizes itself in cycles, a series of thirty normal adult females was observed over a period of three months with reference to their estrous cycles These animals were given from 0.5 cc to 2 cc, each, of sow's follicular fluid, intracardially, on various days of the cycle No primary shock could be demonstrated in animals from the first to the tenth day of the cycle Typical anaphylactic shock was demonstrated in animals from the tenth to the last day of the cycle The anaphylaxis was especially acute, ending in death, in animals that received injections on the last day of the cycle At autopsy, such animals showed extreme congestion of the uterus, ovaries and mammary glands, as well as the typical emphysematous condition of the lungs

To further check these results, fifteen female animals, previously sensitized to sow's follicular fluid were given 15 cc each, of sow's follicular fluid intracardially during the postestrous period. That the animals were desensitized was shown by the total lack of response of thirteen of these animals to this critical dose of antigen. The remaining two animals in the series died with characteristic symptoms of anaphylactic shock (these two animals had just ovulated).

TABLE 1—*Gross Shock as Criterion of Hypersensitivity*

Guinea-Pigs	Follicular Fluid or Protein, and Amount, Used in Sensitization	Time Elapsing after Sensitization, Weeks	Critical Dose of Follicular Fluid or Protein	Time of Administration of Critical Dose with Relation to Last Estrus	Comment
7 female	Sow 0.5 cc	3	Sow 0.5 cc		Typical anaphylaxis and death
3 male	Sow 0.5 cc	3	Sow 0.5 cc		Typical anaphylaxis and death
5 male	Sow 0.5 cc	3	Cow 0.5 cc		Typical anaphylaxis and death
2 female	Sow 0.5 cc	3	Mare 0.5 cc		Severe shock with recovery
2 male	Sow 1.5 cc	3	Mare 3.0 cc		Typical anaphylaxis and death
5 female	Cow 0.5 cc	3	Cow 0.5 cc		Typical anaphylaxis and death
5 female	Sow 0.5 cc	3	Cow 0.5 cc		Typical anaphylaxis and death
1 female	Cow 0.5 cc	3	Mare 0.5 cc		Severe shock with recovery
1 female	Cow 0.5 cc	3	1 we 0.5 cc		Typical anaphylaxis and death
4 male	Cow 2.0 cc	3	Mare 2.0 cc		Moderate shock with recovery
1 male	Cow 2.0 cc	3	Mare 3.0 cc		Typical anaphylaxis and death
5 male	(Never sensitized)		Cow 1.5 cc		No symptom of shock
5 male	(Never sensitized)		Sow 1.5 cc		No symptoms of shock
10 female	(Never sensitized)		Sow 0.7-1.5 cc	10-16 days after	Death
5 female	(Never sensitized)		Sow 0.7-1.5 cc	10-16 days after	No symptom of shock
15 female	(Never sensitized)		Sow 0.7-1.5 cc	1-10 days after	No symptom of shock
15 female	Sow 0.5 cc	3	Sow 0.5 cc	1-5 days after	No symptoms in 13, death in 2
5 male (controls)	Sow 0.5 cc	3	Sow 0.5 cc		Typical anaphylaxis with death
A female	1% casein 0.5 cc	2	0.5% casein 0.5 cc	7 days after	Slight symptoms with recovery
B female	1% casein 0.5 cc	2	0.7% casein 0.5 cc	At estrus	Acute anaphylaxis with death
C female	1% casein 0.5 cc	2	0.7% casein 0.5 cc	5 days after	No symptoms
D female	1% casein 0.5 cc	2	0.5% casein 0.5 cc	10 days after	No symptoms
E female	1% casein 0.5 cc	2	0.5% casein 0.2 cc	At estrus	Acute anaphylaxis with death
F female	1% casein 0.5 cc	2	0.5% casein 0.15 cc	1 day after	Slight symptoms

As a control of the antigenicity of the follicular fluid used, five male animals, sensitized three weeks previously to sow's follicular fluid, demonstrated the typical picture of anaphylaxis on intracardial injection of 0.5 cc of the follicular fluid.

A control series of female guinea-pigs, sensitized to casein, was used to show that this animal is not refractory to anaphylactic shock in general during estrus.

To sum up this section of the work it may be said (1) that the proteins of follicular fluid are antigenic, (2) that the follicular fluids of five mammals thus far studied contain proteins immunologically related, and indeed, as far as determined in this part of the work,

similar, (3) that follicular fluid of the guinea-pig is auto-antigenic, since the primary injection of follicular fluid into female guinea-pigs between the tenth and sixteenth day of the cycle may produce fatal anaphylaxis, and since injection of follicular fluid on the first few days following estrus, into guinea-pigs artificially sensitized to heterologous follicular fluid, elicits no reaction and (4) that female guinea-pigs sensitized to other proteins are more susceptible to anaphylactic shock during and just following estrus than in diestrus

THE BRONCHOSPASM REACTION

It was thought advisable to try the Auer and Lewis⁵ bronchospasm reaction on a series of female guinea-pigs sensitized to follicular fluid in order to represent graphically the differences in degree of sensitivity at various stages of the genital cycle. This difference in sensitivity is understood to be due to the interfering factor of the test animal's own follicular fluid.

TABLE 2—*Results of Test for Bronchospasm Reaction in Guinea-Pigs Sensitized to Follicular Fluid*

Female Guinea-Pig	Follicular Fluid Used	Date of Sensitization	Date of Reaction	Reaction to Injection of Follicular Fluid		Days After Estrus
				Cow	Sow	
992	Sow	3/ 1/28	3/25/28	(Not given)	Positive	0
12	Sow	3/ 1/28	3/17/28	(Not given)	Negative	1
72	Sow	3/ 1/28	3/17/28	(Not given)	Positive	1
449	Sow	2/13/28	3/31/28	(Not given)	Negative	4
25	Cow	2/ 8/28	3/ 3/28	Semipositive	Not given	6
23	Sow	2/13/28	3/ 3/28	Positive	Not given	12
16	Sow	11/19/23	3/21/28	(Not given)	Positive	14
24	Cow	2/ 8/28	3/ 3/28	Positive	Not given	14
111	Cow	2/ 8/28	3/16/28	(Not given)	Positive	15
22	Sow	2/ 8/28	3/ 3/28	Semipositive	Positive	17

The technic involved in this reaction is essentially that of Koessler and Lewis⁶. It consists of sectioning the animal's spinal cord at the level of the medulla, inducing artificial respiration at the rate of 20 per minute, and recording such changes in intrathoracic pressure as occur, due to the excision of the lung, on a revolving drum. In a positive reaction, emphysema occurs immediately, lung excision is prevented, and the writing lever draws a straight line.

Table 2 is made up from data on experiments with ten female guinea-pigs sensitized to either cow's or sow's follicular fluid. Graphs representative of the various reactions are presented, together with characteristic data. In this series, also, the ovaries (and in most instances, the uterus) of all experimental animals were serially sectioned and histologic correlations made.

⁵ Auer, J., and Lewis, P. A. Acute Anaphylactic Death in Guinea-Pigs, J. A. M. A. **53** 458, (Aug 7) 1909

⁶ Koessler, K. K., and Lewis, J. H. Determination of Broncho Spasm in the Guinea-Pig, Arch. Int. Med. **39** 163 (Feb.) 1927

GUINEA-PIG 449—Guinea-pig 449, female, was sensitized with 1 cc of sow's follicular fluid, Feb 13, 1928. A combined bronchospasm, uterine strip reaction was done, March 31, on the fourth day after estral opening (fig 1). In this animal, 0.5 cc and then 1 cc of sow's follicular fluid injected into the external jugular vein caused no anaphylaxis as shown by the pulmonary reaction as well as by the uterine smooth muscle reaction.

Histologic Observations The left ovary contained two large, newly formed corpora each of which still contained rather a large amount of colloid in the core. Many follicles in advanced atresia were seen, and the new follicles showed beginning enlargement but very little cavitation as yet. The right ovary was different in having a large, degenerating yellow body and only one corpus. The uterine horns were still swollen but no longer hyperemic.

GUINEA-PIG 23—Guinea-pig 23, female, was sensitized with 1 cc of sow's follicular fluid, Feb 13, 1928. A bronchospasm reaction was carried out March 3, on the twelfth day after estral opening (fig 2). On the injection of 1 cc of cow's follicular fluid into the external jugular vein, a typical bronchospasm was

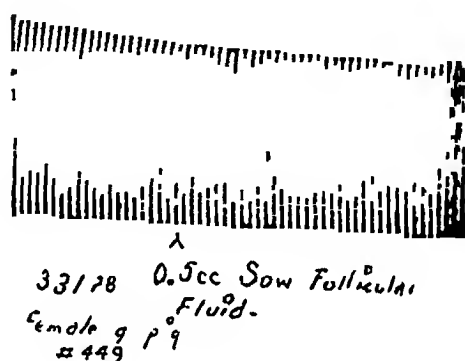


Fig 1 (guinea-pig 449) —The negative result of the Auer-Lewis operation for bronchospasm reaction following the injection of 1.5 cc of sow's follicular fluid into the jugular vein on the fourth day post estrus in a female guinea-pig sensitized to sow's follicular fluid.

obtained immediately. On autopsy, the lungs were greatly distended with emphysema, and the uterine horns were in tonic contracture.

Histologic Observations The left ovary contained about twelve medium-sized follicles all of which appeared healthy, except two, in these, the innermost layer of granulosa cells in some areas showed degeneration. One large corpus showed mitosis of granulosa, as well as of endothelial cells, and early signs of luteal cell degeneration were seen. The right ovary was essentially similar, it had about fifteen medium-sized developing follicles.

GUINEA-PIG 22—Guinea-pig 22, female, was sensitized, Feb 8, 1928, to 0.5 cc of sow's follicular fluid. A bronchospasm reaction was done, March 3, seventeen days after the last estrous opening (fig 3). On intrajugular injection of 0.5 cc of cow's follicular fluid, a semipositive reaction was obtained. Complete bronchospasm occurred when 0.5 cc of sow's follicular fluid was administered by the same route. The fact that only a semipositive reaction was obtained at this stage

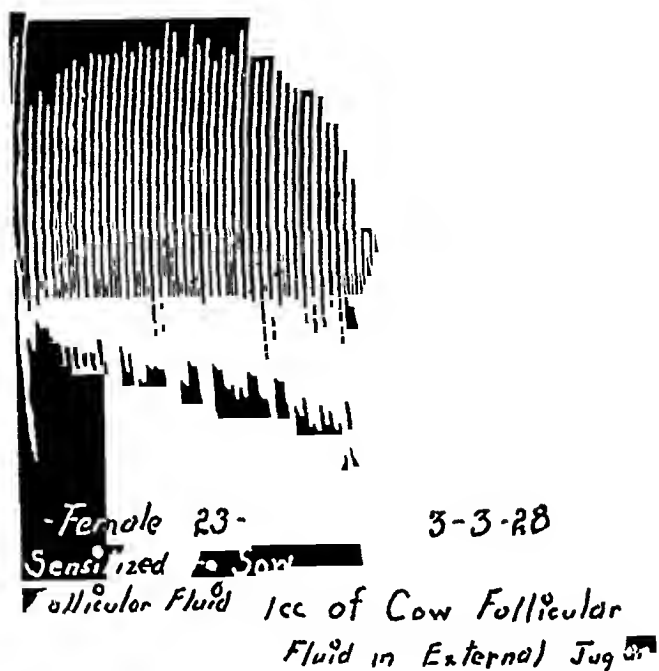


Fig 2 (guinea-pig 23) —The positive bronchospasm reaction following the injection of 1 cc of cow's follicular fluid on the twelfth day post estrus in a female guinea-pig sensitized to sow's follicular fluid

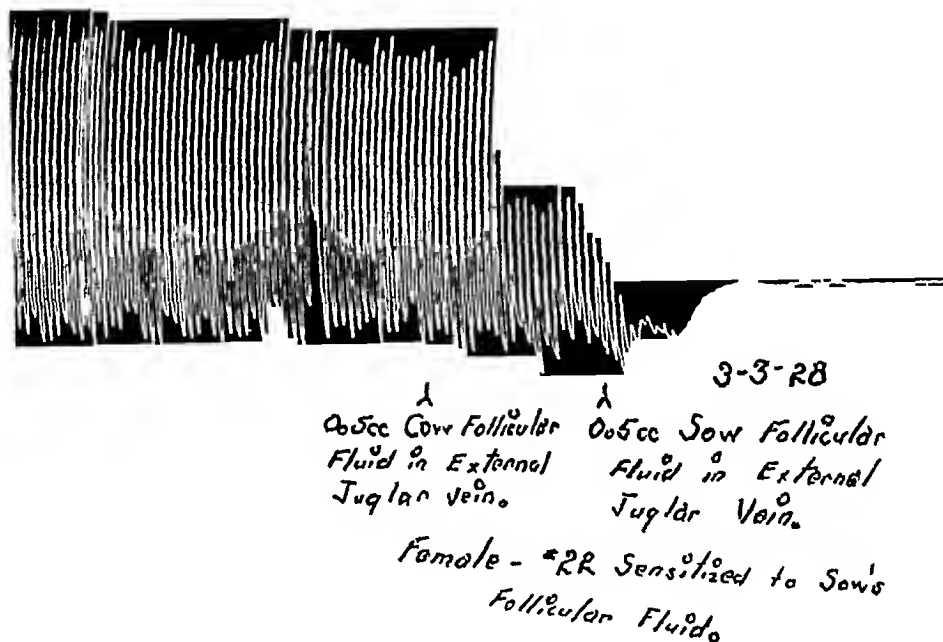


Fig 3 (guinea-pig 22) —The semipositive bronchospasm reaction to cow's follicular fluid, and the positive reaction to sow's follicular fluid on the seventh day post estrus in a female guinea-pig sensitized to sow's follicular fluid

of the cycle with heterologous fluid indicates that desensitization was in progress due to the circulation of the animal's own follicular fluid

Histologic Observations Each ovary contained more than thirty follicles, most of which were in various stages of atresia, and only one of which would have matured and ruptured. Three corpora in an early stage of degeneration were seen in the left ovary, while the right contained one.

GUINEA-PIG 24—Guinea-pig 24, female, was sensitized Feb 8, 1928, with 0.5 cc of cow's follicular fluid. A bronchospasm reaction was tried fourteen days after the estral opening (fig 4). On injection of 3 cc of a 1:3 solution of cow's follicular fluid in saline solution, which was allowed to run slowly into the external jugular vein a bronchospasm occurred within four minutes.

Histologic Observations Each ovary contained more than thirty follicles, the majority of which showed varying degrees of atresia. Two healthy

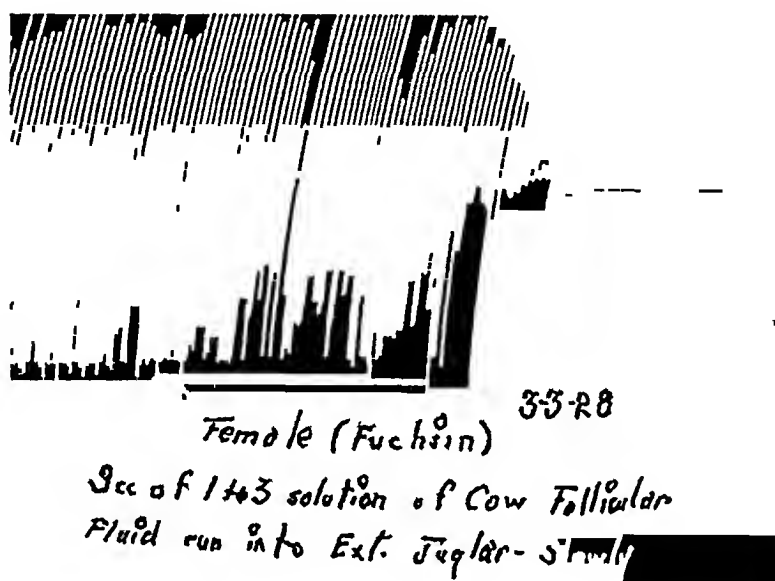


Fig 4 (guinea-pig 24) —The positive bronchospasm reaction to cow's follicular fluid on the fourteenth day post estrus in a female guinea-pig sensitized to cow's follicular fluid

follicles were nearly mature. The earliest stage of corpus degeneration was observed in two corpora in this ovary. The endothelial cells seemed to surround degenerating luteal cells.

It developed from this small series of animals that in female guinea-pigs sensitized to foreign follicular fluid an extremely sensitive immunity balance may be readily effected by the test animal's ovarian activity directly referable to the follicular phase. A series of normal female guinea-pigs in which bronchospasm has been produced on primary injection is now being worked with, and it is with these, rather than with artificially sensitized animals, that we hope to explain the finer mechanism governing antigen-antibody balance in the genital cycle.

THE SCHULTZ-DALE REACTION

Attention was next given to the Schultz-Dale⁷ reaction with isolated strips of uterus and gut. It was hoped that in this experiment differentiation might be made immunologically between follicular fluids of different animals.

Ten female guinea-pigs were used in this series, each being sensitized to either sow's or cow's follicular fluid and observed as to its estrous cycle. Like certain animals in the experiments with gross anaphylaxis, some of these animals were found refractive at certain stages of the cycle. This was further evidence of the desensitizing action of the test animal's own follicular fluid and of the interrela-



Fig 5 (guinea-pig 24) —A section of the right ovary

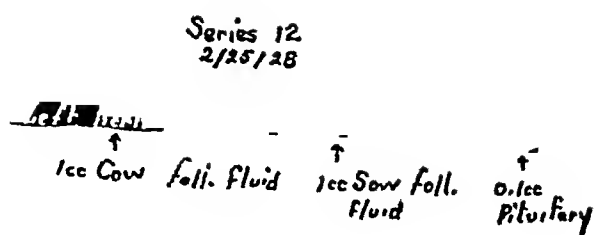
tionship of the heterologous fluids. It was possible to show that the same degree of sensitivity did not necessarily prevail in both uterine horns, as for example

GUINEA-PIG 150—Guinea-pig 150, female, was sensitized to sow's follicular fluid (1 cc injected intraperitoneally), Feb 13, 1928. The Schultz-Dale reaction was done February 25, the first day of the cycle (fig 6, A, B and C).

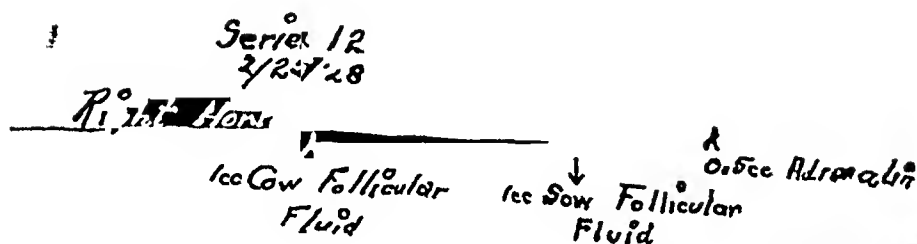
Dale Reaction. The uterine horns were large and swollen, but not hyperemic. The left uterine horn was refractory to 1 cc of cow's follicular fluid and to 1 cc of sow's follicular fluid, but reacted typically to 0.1 cc of solution of pituitary. The right horn gave no reaction to 1 cc of cow's follicular fluid, but a typically positive Dale reaction to 1 cc of sow's follicular fluid. It was relaxed with 0.5 cc of epinephrine hydrochloride. A strip of gut did not react to cow's but did to sow's follicular fluid. It was relaxed with epinephrine.

⁷ Schultz, W. H. Physiological Studies in Anaphylaxis, *J. Pharmacol. & Exper. Therap.* 1:549, 1909-1910.

A



B



C

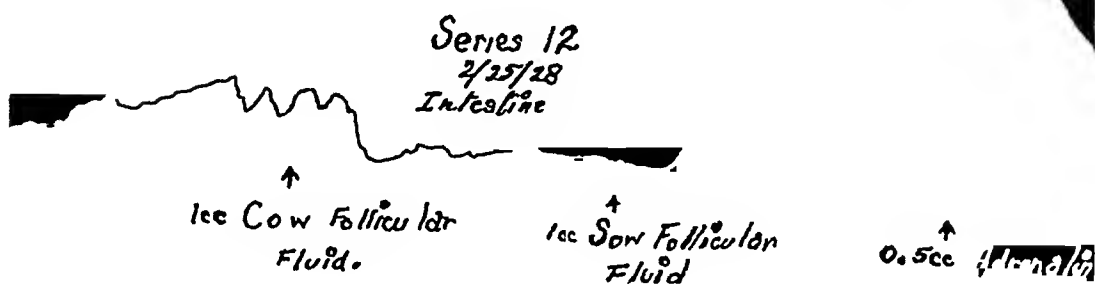


Fig 6 (gumea-pig 150) —A, the Dale reaction of the left horn of the uterus on the first day of the estrous cycle in a gumea-pig sensitized to sow's follicular fluid (1) to cow's follicular fluid, (2) to sow's follicular fluid and (3) to pituitrin B, the Dale reaction of the right horn to (1) and (2) C, the Dale reaction of intestine to (1) and (2)

Histologic Observations On section, the left ovary was found to be double the right in size. It contained three large ripe follicles bulging with fluid, three degenerating yellow bodies and many follicles in advanced stages of atresia. Figure 7 represents a section through the ovary and shows two prerule follicles and many atretic follicles. The right ovary contains only one yellow body, many atretic follicles and three healthy follicles not nearly as large as those in the left.

Furthermore, following ovulation the same degree of sensitivity need not exist in distal and proximal portions of the same uterine horn. To illustrate

GUINEA-PIG 5—Guinea-pig 5, female, was sensitized to sow's follicular fluid, Jan 31, 1928. A Dale reaction was done, February 19, the fourth day of the cycle (fig 8, A, B and C).

Dale Reaction On exposure of the uterus of this animal, the right horn was seen to be white, not swollen, and apparently in a resting condition. The distal half of the left horn was as the right, but its proximal half was hyperemic,

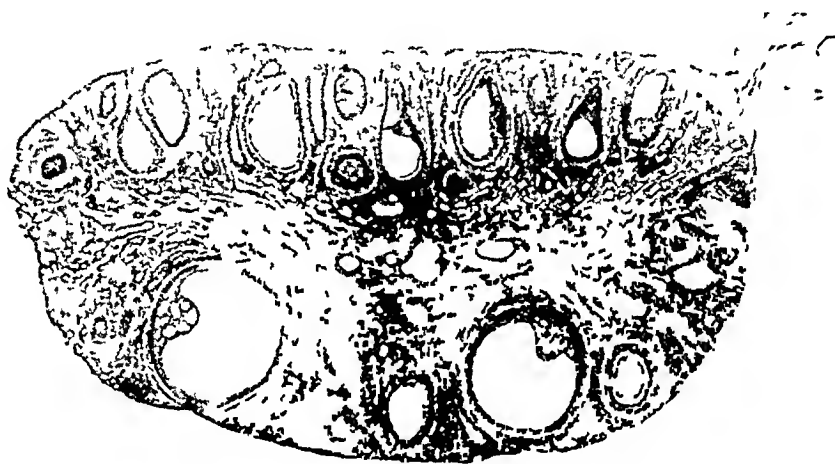


Fig 7 (guinea-pig 150) —A section of the left ovary

swollen and apparently still "in reaction." Tracings were accordingly made with the whole right horn, and with the separated distal and proximal halves of the left. As shown in the curves obtained (fig 8), the right horn did not react to 1 cc of cow's follicular fluid, but did to 0.5 cc of sow's follicular fluid. The distal portion of the left horn reacted likewise, but the proximal half was refractive to both cow's and sow's follicular fluid, it did react, however, to pituitrin.

Histologic Observations The left ovary showed a medium-sized recently formed corpus. Several follicles in advanced stages of atresia were seen, and two medium-sized follicles which had neither ruptured nor degenerated. Two small epithelial-lined cysts were present. The right ovary was essentially the same as the left, except that the new corpus was about half as large.

Positive smooth muscle reactions were readily elicited in both uterine and gut strips with heterologous follicular fluids when the animal's own ovary was in its lutein phase (fig 9). At this time, apparently, there is no absorption of the soluble substance that later in the cycle desensitizes the animal.

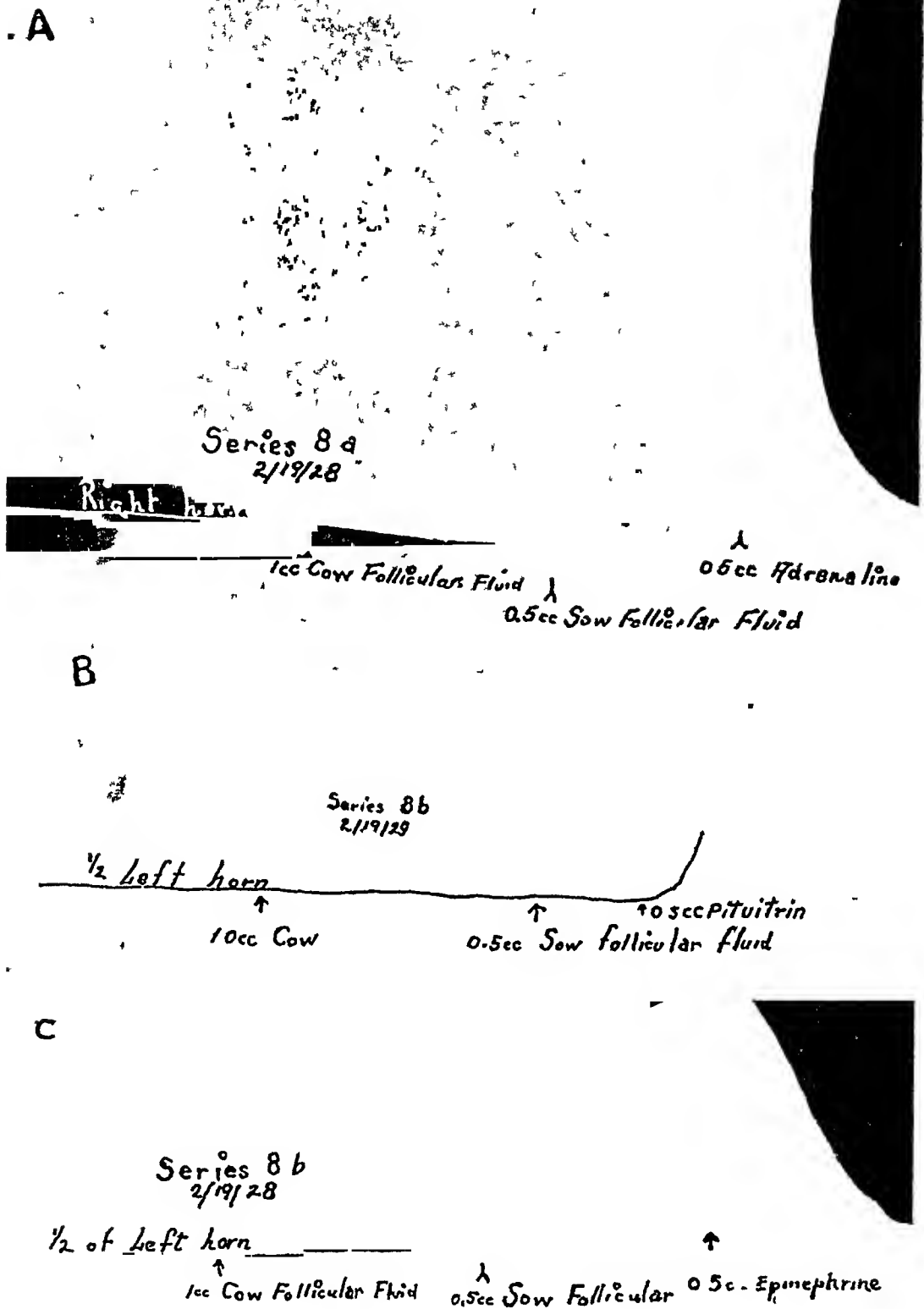


Fig 8 (guinea-pig 5) — A, the Dale reaction of the right horn of the uterus on the fourth day of the estrous cycle in a guinea-pig sensitized to sow's follicular fluid (1) to cow's follicular fluid and (2) to sow's follicular fluid B, the Dale reaction of the left horn of the uterus, proximal half to (1) and (2) C the Dale reaction of the distal half to (1) and (2)

After the fourteenth day of the cycle, however or at the commencement of the follicular phase, it was customary to find the smooth muscle refractive not only to heterologous antigen, but also to the follicular fluid used in sensitization (fig 10). As did the work with gross

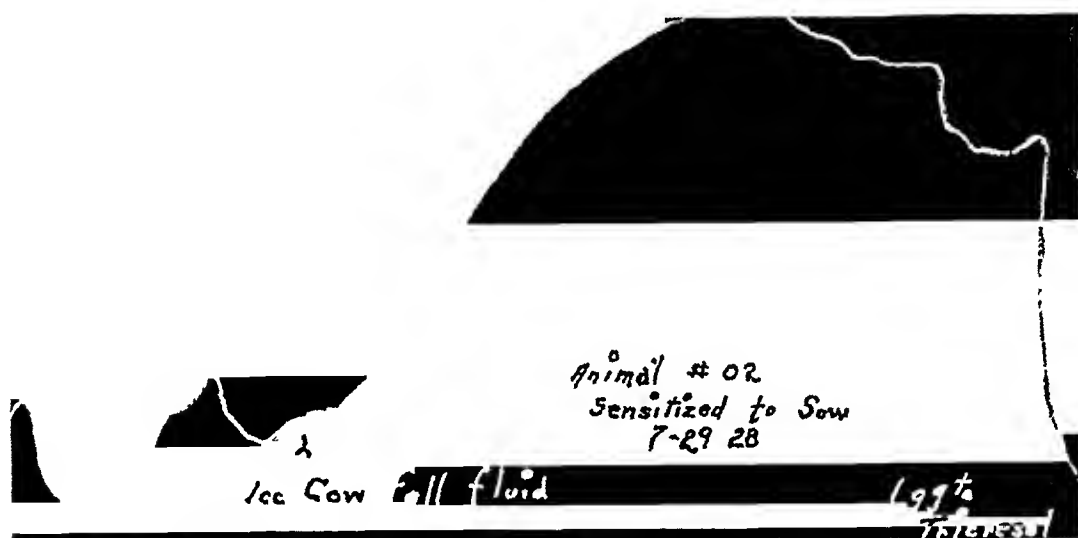


Fig 9 (guinea-pig 02) —The Dale reaction of the uterus of a sensitized guinea-pig on the fourteenth day of the cycle, when its ovaries were in the lutein phase

Fig 10 (guinea-pig 281) —The Dale reaction of the uterus of a sensitized guinea-pig on the sixteenth day of the cycle, when its ovaries were at the commencement of the follicular phase

anaphylaxis, the work with smooth muscle showed that the test animals' own follicular proteins, or the "specific soluble substances" of the ovary, are apparently responsible for a gradual cyclic desensitization which persists for only a short time

A series of twelve virgin guinea-pigs, not previously sensitized to heterologous follicular fluid, was then used. It was found possible to elicit typical Dale reactions in the uterus and gut with heterologous follicular fluids at certain stages of the cycle, showing that these animals had become sensitized to their own ovarian proteins (fig 11)

COMMENT

While this study merely adds another relatively nonspecies-specific antigen to a gradually enlarging list (casein, fibrinogen, crystalline lens, ovoproteins, etc.), we believe that it should be possible to carry this work to a point which may result in the removal of some of the vagueness that accompanies our present conceptions of the functions of the sexual endocrine substances.

It is apparent from the data presented that there is some substance, probably protein in nature occurring in the various mammalian follicular fluids studied that is capable of producing the anaphylactic syn-



Fig 11 (guinea-pig 024) —The Dale reaction of the uterus of a normal animal on the tenth day of the cycle

drome in guinea-pigs. We are unable to state at the present time whether this substance is the same in each of these species or whether the proteins of these fluids are sufficiently related chemically to give rise to identical immunologic phenomena.

There is, however, no doubt but that these animals are sensitized and desensitized generally during various periods of their sexual cycle by their own follicular fluid. This phenomenon becomes more apparent when local immunization is considered. Following ovulation and liberation of the follicular fluid, both uterine horns, or even part of a horn, may become desensitized, depending on several factors, chief among which are the amount of follicular fluid liberated and in which ovary ovulation occurs. Desensitization may not proceed evenly, so that one horn or even a part may regain sensitivity before the rest of the uterus.

It would appear, however, that a cyclic hypersensitiveness to follicular fluids, as well as to the "test-substances," is much in evidence in the female guinea-pig. The degree of reactivity of the uterus and

gut seems to be based on an extremely delicate balance between the animal's own follicular fluid and antistances

While toxicity of ovarian substances has long since been demonstrated, we are not aware that this subject has been given much attention from an immunologic standpoint. Champy and Gley, in 1927 reported that as early as 1912 they had demonstrated what they termed "tachyphylaxie" in female rabbits into which extracts of corpus luteum or whole ovary had been injected. These animals died, and on autopsy showed extreme congestion of the genital organs and the mammary apparatus. We have observed these same phenomena in normal female guinea-pigs on intracardial injection of foreign follicular fluid. Other workers have been more obscure as to the source of the toxic factor. In our work as high as 5 cc of sow's, cow's, or mare's follicular fluid, given intracardially, has elicited no toxic symptoms in male guinea-pigs at least 6 weeks old. Animals of both sexes younger than this may show shock on primary injection of as little as 0.5 cc of these fluids, and this is also true of adult females at a definite stage of the estrus cycle.

SUMMARY

Male guinea-pigs have been used to show by means of gross anaphylactic reactions the relationship of various mammalian follicular fluids. These animals when sensitized to sow's or cow's follicular fluid responded with the typical anaphylactic syndrome on the subsequent injection of sow's, cow's, ewe's, or mare's follicular fluid. None showed ill effects from primary intracardial or intraperitoneal injection of these fluids.

The use of the female guinea-pig introduced a new factor, namely, the effect of the animal's own follicular fluid on the condition of hypersensitivity to heterologous fluids. Our attention was called to this factor, first, by a number of fatalities ensuing on both intraperitoneal and intracardial primary injections into mature female guinea-pigs, of sterile follicular fluid harmless to adult male guinea-pigs, and second, by the fact that female guinea-pigs previously sensitized with impunity to heterologous follicular fluid showed not the slightest symptom of anaphylaxis on reinjection after the proper interval, provided they had recently ovulated, as determined by the condition of their vaginæ.

Knowing that desensitization in the broad sense of the term may be brought about in various ways, and especially by affecting the autonomic nervous system, it was deemed necessary to control this second observation by determining whether just postovulatory nervous state of the guinea-pig was such as to render it refractive to a critical injection of some specific protein to which it was sensitized, other than follicular fluid. Consequently there was included a small series of animals sen-

sitized to casein, which were not refractive to critical injections just following ovulation, but on the contrary more susceptible

Of a series of fifteen guinea-pigs sensitized to foreign follicular fluid, thirteen are reported refractory to second injection just following estrus. Judging from the histologic observations in the two that suffered shock, one may conclude that ovulation had preceded the critical injection too soon to allow for absorptions of the follicular fluid and general desensitization.

Attention was next turned to animals showing acute shock on primary injection of foreign follicular fluid. It was found that this reaction might be elicited in female guinea-pigs at certain times during the cycle.

By means of the Schultz-Dale technic, it was possible to show that guinea-pigs sensitized to foreign follicular fluids are rendered temporarily desensitized by the elaboration of the animal's own follicular fluid. The same technic shows that normal female guinea-pigs become sensitized to their own follicular fluid at certain times during the estrous cycle.

CONCLUSIONS

The follicular fluids of the four mammals studied (sow, cow, mare, ewe) are closely related immunologically, they are similarly related to the follicular fluid of the experimental animal, the guinea-pig.

Guinea-pig follicular fluid is auto-antigenic.

Guinea-pigs artificially sensitized to follicular fluid proteins are temporarily desensitized by the liberation of their own follicular fluid.

Fatal anaphylaxis may be produced at a definite time, in normal guinea-pigs, on primary injection of heterologous follicular fluid.

PRIMARY CARCINOMA OF THE URETER

REPORT OF A CASE AND REVIEW OF THE LITERATURE¹

RIGNEY D'AUNOY, MD
AND
ADELAIDE ZOELLER, MD
NEW ORLEANS

REPORT OF CASE

History—Mrs F L, white, aged 59, complained of blood in the urine. It had been present for a week before examination. Her familial history and her past history were unimportant. The results of physical examination were negative. A slight secondary anemia was present. The Wassermann reaction of the blood was negative. Repeated examination of the urine showed the presence of a trace of albumin with red blood cells and leukocytes microscopically. Ureteropyelograms showed ptosis of the right kidney with irregularity in filling, dilatation and kinking of the right ureter. The filling defect, 15 cm below the lower border of the ileum, according to the roentgenologic report of Dr Amedee Granger, was most probably the result of a new growth. Reexamination resulted in similar observations and conclusions.

Under spinal anesthesia, ureterectomy was performed by Drs Lindner, Ochsner and Mahles. Forty days later, right nephrectomy was performed. Recovery after both procedures was uneventful.

Gross Observations in Ureter—The specimen was a portion of the ureter measuring 75 cm in length. Near one end was a fusiform dilatation (fig 1) 4 cm in length and 0.5 cm in its largest diameter. Above and below this dilatation, the ureteral wall was thin and elastic, presenting no gross changes externally. At the site of the enlargement, the ureteral wall was considerably thickened, nonelastic and firm. When the ureter was opened, a tumor was found impinging on and practically occluding its lumen, at the site of the externally noted enlargement (fig 2). The tumor was attached to the ureteral mucosa by a broad base and presented numerous, dense, papillalike projections varying in size from hairlike strands to strands from 2 to 20 mm thick. These papillary projections were densely compact, some of the larger ones showing at their free ends cauliflower-like protuberances. At the periphery of the growth, some of the smaller papillae could be removed by plucking. After such removal, the ureteral wall revealed a pitted and roughened reddish-brown surface. For the most part, however, removal by plucking was not possible, the papillary projections being firmly adherent and apparently a part of the ureteral mucosa.

Microscopic Observations in Ureter—Cross-sections of the tumor mass showed papillae composed of epithelial cells and separated by thin layers of vascular connective tissue. Here and there adjacent papillae showed fusion of epithelial elements with the formation of solid sheets of cells. The individual epithelial cells were densely packed, mostly large and irregular in shape, though generally polyhedral, many showed pyknotic nuclei. Mitotic figures were noted. For the most part, the wall of the ureter was not penetrated, but here and there aggregates of irregularly shaped, intensely staining epithelial cells were noted invading the

* Submitted for publication, Sept 3, 1929.

* From the Department of Pathology of the Charity Hospital.

various layers of the ureter, especially the submucosa. Some such aggregates were surrounded by round cells. At the bases of many papillae, cell polarity was lost.

Gross Observations in Kidney—The specimen was a kidney opened through the pelvis by an incision in the longitudinal diameter of the organ. It weighed 95 Gm. and was rather flabby. The external surfaces varied from brownish red to grayish red and were rather smooth, moist and glistening, with small petechial hemorrhages appearing through the capsule. In the region of the pelvis there was some fat. The capsule stripped with some difficulty, revealing a rather granular surface varying from brownish red to grayish red, the darker areas



Fig. 1—External appearance of a tumor-containing ureter

evidently representing capillary hemorrhages. The internal surfaces revealed by sectioning varied from grayish pink to grayish brown and showed obliteration of normal markings, with an extremely thin and flat cortex wherever discernible. The pelvis was rather dilated and irregularly shaped, its mucosa being granular and presenting throughout minute petechial hemorrhages. Such small hemorrhages were also noted throughout the organ. Careful sectioning failed to reveal any new growth or stone formation.

Microscopic Observations in Kidney—Microscopic study of numerous sections of the kidney showed generally the same changes. All the blood vessels were thickened and engorged. The tubular and glomerular lining cells were generally the seat of cloudy swelling and fatty metamorphoses. Most of the glomeruli were

small and adherent to their capsules and lay close together. Many presented degenerative changes, some having undergone marked hyalinization, some few, however, were evidently undergoing hypertrophic compensatory changes. Numerous atrophic tubules were seen. A highly cellular connective tissue stroma was noted, containing inflammatory elements.

REVIEW OF THE LITERATURE

Reports of primary carcinoma of the ureter have appeared in medical literature since 1879. Hektoen¹ in reporting a case in 1896, referred to two earlier ones. Albaran, in a review of the literature of



Fig 2—Low power photomicrograph showing early invasion of ureteral wall with loss of basal cell polarity.

primary ureteral tumors in 1902, compiled 10 case reports, of which five dealt with carcinomatous, two with papillary and three with non-papillary growths. Richter² in 1909 reviewed the literature of primary carcinoma of the ureter and found eleven reports of cases. Butler,³ in

1 Hektoen, L. Primary Carcinoma of the Ureter, *J A M A* **26** 1115 (June 6) 1896.

2 Richter, T. Primäres Carcinom des rechten Ureters, *Ztschr f Urol* **3** 416, 1909.

3 Butler, F. A. A Case of Primary Carcinoma of the Ureter, *Clifton M Bull* **2** 48, 1914.

1914 found nineteen previous reports of cases. Judd and Struthers,⁴ in 1921, found twenty-five and added their own. McCarthy and Meeker,⁵ in 1923, in the last complete review published, added a number overlooked in previous summaries, which, together with their own brought the total to thirty-three. We have been able in a thorough search to find a total of forty-seven reports of cases, including a few overlooked in previous reviews. These, together with the report we have now

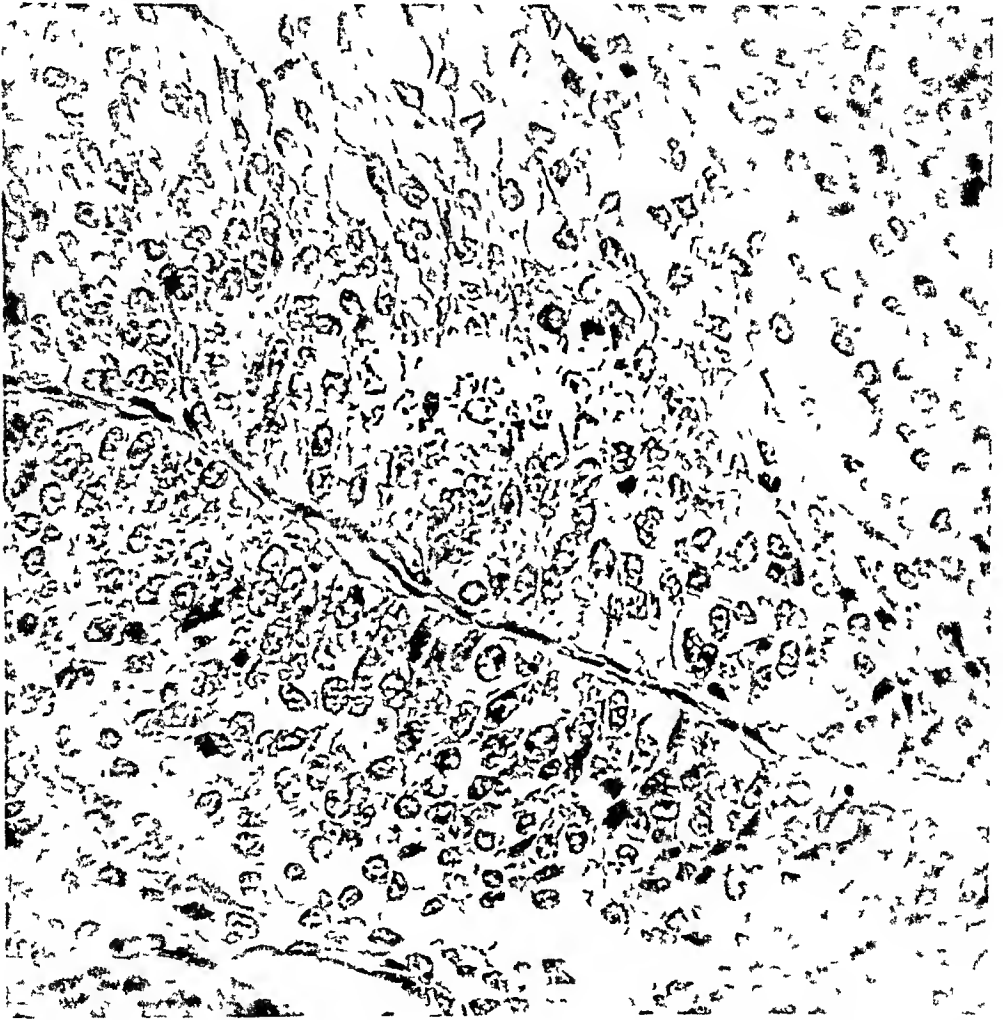


Fig. 3—High power photomicrograph showing cell polymorphism, pyknosis, some mitosis and beginning fusion of cell elements

recorded bring the total number of reports of primary carcinomas of the ureter to forty-eight. The salient features of these reported cases are tabulated in table 1.

4 Judd, E. S., and Struthers, J. E. Primary Carcinoma of the Ureter. *J. Urol.* 6: 115, 1921.

5 McCarthy, J. F. and Meeker, L. H. Primary Carcinoma of the Ureter, Report of a Case and Review of the Literature, *J. A. M. A.* 81: 104 (July 14) 1923.

In critically reviewing the various reports, much difficulty was encountered in the histologic classification of the tumors, owing principally to the varying and at times bizarre nomenclatures adopted by the authors. We have therefore classified them, for the most part, on the basis of their papillary or nonpapillary character. Again, the title of a report would indicate that the tumor under consideration was malignant, but the body of the article and the histologic description of the growth, when given, made its classification as malignant dubious. Therefore, with the exception of Kleinschmidt's⁶ case, we have not included any case in the report of which the author does not clearly state that there was enough histologic evidence to classify the tumor as malignant or in which the histologic description of the tumor or the mechanical reproduction of sections thereof does not make its classification as malignant apparent. The exception in Kleinschmidt's case is made because of Kummel's⁷ statement that repeated histologic examinations of the growth revealed it to be an early type of malignant tumor. On this basis, we have been obliged to exclude such tumors as Takahashi's,⁸ Dózsa's⁹ case III and Cassuto's¹⁰. Histologic study of these tumors, especially of the latter's, in view of its apparent recurrence and extension, may possibly have revealed malignancy. However, as no record of such examinations occurs in the reports, the tumors these observers encountered must be regarded as, at most, suspicious growths primarily either of the ureter or of the kidney pelvis and ureter, and cannot with justification be included in this summary of proved primary carcinomas of the ureter.

Incidence with Regard to Age and Sex —Of the forty-eight ureteral tumors reported, twenty-five occurred in males, twenty-three in females (table 2). The earliest age at which a case occurred in men was that of 35 years, two cases are on record. In women, the earliest age at which a case occurred was that of 36. The oldest age at which a case occurred in men was that of 74, in women, that of 89. The greatest number of cases (fourteen) in both sexes occurred in persons between the 60th and the 70th years. In men, the greatest occurrence for any decade was that between the 60th and the 70th years (eight cases), in

6 Kleinschmidt, R. Beitrag zur Kenntnis der primären Uretertumoren, Deutsche Ztschr. f. Chir. **191** 103, 1925.

7 Kummel, H. Ueber Nierenbecken und Uretergeschwulste, Monatschr. f. Harnkrankh. u. sex. Hyg. **2** 195, 1928.

8 Takahashi, A. Kasuistische Mitteilung der merkwürdigen Uretergeschwulste die bei der cystoskopischen Untersuchung beobachtet wurden, Ztschr. f. urol. Chir. **22** 172, 1927.

9 Dózsa, E. Weitere Beiträge zur Kenntniss Zottengeschwulste des Nierenbeckens und Ureters, Ztschr. f. urol. Chir. **22** 81, 1927.

10 Cassuto, A. Uro-pyonéphrose due à un papillome implanté sur le meat urétéral, Lyon chir. **24** 253, 1927.

TABLE 1—Data in 48 Recorded Cases of Primary Carcinoma of the Ureter

Author, Year	Age of Patient	Sex	Location of Carcinoma	Histologic Classification	Extension by		Duration
					Continuity	Metastases	
Wiesing and Blumgen 40 468, 1879	41	F	Right upper third	Nonpapillary		Peritoneum, perirectal glands	Some time
Davis ¹⁶	53	M	Left lower third	Nonpapillary	Rectum bladder	Liver	2 years
Tona Centralbl f allg Path u Anat 5 659, 1894	43	F	Left lower third	Papillary			
Voeleker Tr Path Soc London 46 133, 1895	68	M	Left lower third	Papillary	Periureteral	Liver, retroperitoneal glands, lungs	1 year
Rundie ¹¹	46	M	Right lower third	Squamous cell	Seminiferous vesicles	Liver lungs	
Hektoen ¹	50	F	Right lower third	Nonpapillary	Hemipneumothorax		8 months
Toupet and Guenoit Bull Soc anat de Paris 73 678 1898	59	F	Left diffuse	Papillary			
Minch Pest med chir Pre-se 24 911, 1902	60	F	Right lower third	Squamous cell	Vagina bladder		
Gerstein Inaug Diss., Kiel, 1902	67	M	Right lower third	Nonpapillary	Bladder	Lungs kidneys	9 months
St Thomas Hosp 12 96 1903	69	M	Left lower third	Papillary		Perivertebral glands to diaphragm	6 months
Adler Monatschr f urol 10 129 1905	69	M	Left lower third	Papillary corniform		4th lumbar vertebra	8 weeks
Metcalf and Safford ¹⁴	47	M	Left lower third	Nonpapillary	Serum	Kidney	Years
Vorpahl ²⁵	60	F	Right lower third	Nonpapillary squamous cell		Liver lungs	1 year
Zaroni ¹⁴	36	F	Right lower third	Squamous cell			7 months
Richter ⁷	80	F	Right lower third	Papillary		Adjacent glands	3 months
Paschkis Wien klin Wchnschr 23 361, 1910	65	M	Left lower third	Papillary	Periureteral	Adjacent glands	4 months
Israel and Lowenstein Berl klin Wchnschr 47 2381, 1910	56	F	Left multiple	Papillary		Spleen glands	10 years
Chevassu and Moeck Bull et mon Soc Nat de chir 18 522, 1912	53	M	Left middle	Papillary			5 weeks
Charu Ztschr f urol 18 672 1914	54	F	Left middle	Papillary			3 months
Butler ⁵	53	M	Right middle	Squamous cell	Periureteral		19 months
Schmitt J Cancer Research 1 461, 1910	55	F	Left upper third	Nonpapillary	Vertebra 11 dorsal 3 lumbar	Liver	9 months
Spies ²⁶	41	F	Right lower third	Nonpapillary	About ureteral orifice	Lungs, glands	9 weeks

TABLE 1—Data in 48 Recorded Cases of Primary Carcinoma of the Ureter—Continued

Author, Year			Age of Patient	Sex	Location of Carcinoma	Histologic Classification	Extension by		Duration
							Continuity	Metastases	
Finsterer	Wien klin Wchnschr	28 81, 1927	35	M	Left lower third	Papillary	Papillary growths		4 years
Van Cappel	Butr 7 klin Chir	40 138, 1916	46	F	Right middle	Papillary			14 years
Hofmann	Ztschr f urol	15 369, 1916	35	M	Left lower third	Papillary (early)	Bladder		4 years
Knack	Deutsche med Wchnschr	44 982, 1918	73	M	Left middle and lower third	Papillary	Bladder		
Qunby	J Urol	4 439, 1920	40	F	Left middle	Nonpapillary	Peri-ureteral		3 weeks
Rathbun	Internat Surg	6 232, 1920	40	M	Left middle	Papillary			2 years
Walker ²⁷			38	M	Right entire	Papillary	Peri-ureteral	Liver, abdomen	6 years
Judd and Struthers ⁴			48	M	Left lower third	Papillary			2 years
Suter	Ztschr f urol Chir	10 322, 1922	65	M	Left lower third	Nonpapillary	Peri-ureteral		10 months
Idem			64	F	Right lower third	Nonpapillary			2½ years
Aschner	Surg Gynec Obst	35 749, 1922	38	M	Right upper third	Squamous cell			9 months
Meeker and McCarthy ⁵			49	M	Right entire	Papillary		Genital, liver, lungs, glands, etc	6 months
Kraft ²¹			52	F	Left middle and lower third	Papillary (early)			4 months
Crance and Knieker	J A M A	82 1930 (June 14) 1924	42	F	Right lower third	Nonpapillary			
Kretschmer	Surg Gynec Obst	38 47, 1924	74	M	Right lower third	Nonpapillary		Carcinoma of hip 20 years previously	5 weeks
Papin	J d'urol	17 4, 1924	57	M	Right upper third	Nonpapillary			2 months
Marz	J Urol	12 49, 1924	69	F	Right lower third	Nonpapillary	Had been operated on for carcinoma of uterus 10 years before		5 months
Morse, H D	J Canadian M A	15 902, 1925	54	M	Right lower third	Papillary			1 year
Kleinschmidt ⁶			65	M	Right lower third	Papillary			8 days
Stewart ¹⁷			75	F	Right upper third	Papillary			8 months
Posner	Geburtsch u Gynak	75 86, 1926	66	F	Right lower third	Papillary			8 months
Glas ²²			71	F	Right lower third	Nonpapillary	Periureteral and wall of opposite ureter		10 weeks
Viethen	Ztschr f urol	21 605, 1927	45	M	Left middle	Papillary			Several years
Hunt	S Clin Amer	7 1464, 1927	67	M	Right lower half	Papillary			1 years
Player ²³			65	F	Left upper third	Papillary	Peri-ureteral		
Authors' case			59	F	Right lower third	Papillary			1 week

women, that between the 50th and the 60th years (six cases) and that between the 60th and the 70th years (six cases)

Sites of Tumors—Twenty-six tumors were of the right ureter, twenty-two of the left (table 3) The largest number occurred in the lower third of the ureter eighteen such tumors occurring in the right and eleven in the left ureter The upper third of the ureter was less frequently involved, four times on the right side and twice on the left

Types of Tumors—Twenty-eight of the tumors were of frank papillary type and were so designated in the reports The remaining were classified as nonpapillary or, at least, their papillary features were not prominent For these, such designations as "medullary" "epithelial" "transitional celled," "carcinoma simplex" "tubular," "adenomatous," "squamous," "mucous membrane carcinoma," "cylindric," "encephaloid," "keratoid" are encountered We have not found it pos-

TABLE 2—Incidence of Primary Carcinoma of the Ureter with Regard to Age and Sex

	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	Total
Male			4	6	5	8	2	0	25
Female			1	6	6	6	2	2	23

TABLE 3—Sites of the Occurrence of the Tumors

	Upper Third	Middle Third	Lower Third	Diffuse or Multiple	Total
Right ureter	4	2	18	2	26
Left ureter	2	5	11	1	22

sible to classify the growths except as regards their papillary characteristics in general

Etiology—The etiology of ureteral tumors is unknown, although many theories attempting to account for their occurrence have been advanced Of these, the following deserve mention

- 1 Leukoplakia, with an acceptance of leukoplakia as a process primarily and essentially malignant
- 2 Leukoplakia with intervening malignant metamorphosis
- 3 An ascending epidermization
- 4 Cell inclusions or enclavements occurring during embryonal development and in adult life
- 5 Mechanical irritation
- 6 Chronic inflammatory irritation
- 7 So-called benign hyperplasia of the mucous membrane (diffuse papillomatosis, discrete papilloma formation)

Most German authors lay great stress on leukoplakia, so often encountered in the renal pelvis and ureters, either considering the leukoplakia itself as a malignant or premalignant manifestation or assuming that it is capable of an intervening malignant metamorphosis. Some even assume a predisposition of the tissues of the entire urinary tract to pathologic growths. That this leukoplakia so often stressed as etiologically important is not extremely important so far as primary ureteral tumor is concerned, is suggested by the fact that the ureter alone is rarely involved in leukoplakic processes, there being generally a concurrent involvement of the renal pelvis and bladder. However, leukoplakia when involving the ureter has been encountered only unilaterally, no case of frank bilateral primary ureteral malignancy is recorded, although numerous cases of tumor of the bladder and renal pelvis with coexistent ureteral tumor have occurred.

Tumors of frank ectodermal origin, such as were first described by Rundle¹¹ and since by many others, are possibly best explained on the basis of developmental abnormalities, although the interesting and to some extent enticing theory of metaplasia must be considered in accounting for them. When one considers that after the formation of the mesoblastic pronephron the ectodermal cloaca comes in contact with and invaginates into it, one can satisfactorily account for the accidental carrying of displaced ectodermal cells to various parts of the urinary tract, with subsequent development of such cell nests or enclavements into tumors as a result of factors and processes at present not understood. This may be satisfying in showing the sites at which such tumors may occur, but certainly this little satisfies one as to the all important questions as to how and why the tumors occur even in such cell displacements.

Distinct from this concept of development in cell nests produced as the result of embryonal abnormalities is the suggestion of many authorities that the so-called islands of Brunst are the points of departure for neoplastic processes in the ureter. These, as is well known, consist of epithelium reaching downward from the mucous membrane and giving rise to isolated aggregates of epithelial cells below the covering epithelium. To some, these islands must be considered as the expression of an inclination to proliferation normally possessed by the mucosa of the ureter, this inclination seemingly increasing with age and with the presence of chronic inflammatory processes. Undoubtedly, the observations of Harbitz¹² and Boccolari¹³ indicate that this liability of the

11 Rundle, H. Epithelioma of Ureter Causing Hydronephrosis, *Tr. Path. Soc. London* **42** 128, 1896.

12 Harbitz, F. Ureteritis cystica, *Norsk Mag. f. M. Sc.* **71** 126, 1918.

13 Boccolari, Segolini A. Ureterite cistica e fibro-papilloma cistico dell'ureter in bovini, *Gior. di med. vet. Torino* **77** 132 and 161, 1928.

mucous membrane of the ureter to form epithelial islands may result in either cyst or tumor formations, again through factors and by processes not fully understood

Mechanical irritation playing as it does at times, such an important rôle in the production of tumors, the ureteral neoplasm might be expected frequently to exist as a concomitant of calculus formation. Such, however, is not the case, though Zironi¹⁴ and Metcalf and Safford¹⁵ among others, have inclined to the view that there is an etiologic relationship between calculi and neoplasms of the ureter. In only six of the forty-eight cases have calculi been present. Undoubtedly, as in Metcalf and Safford's and Davy's¹⁶ cases, for example, the constant irritation caused by an impacted calculus must be considered as an important predisposing factor. However, as Stewart¹⁷ pointed out and as is well exemplified in Le Dentu's¹⁸ case, though this was one of a benign tumor, the concretions may develop subsequently to the ureteral obstruction and urinary decomposition occasioned by the tumor. Again, tumor cells themselves may act as nuclei for the production of stones. Most of the cases of tumor with coincident lithiasis were cases of squamous usually cornified epithelial neoplasms of the upper urinary tract and not of the lower tract. That other irritants can possibly cause tumor formation must be admitted especially in view of Leone's¹⁹ experimental demonstration thereof with tar.

That the so-called papillomas so often encountered in the renal pelvis, ureter and bladder play an important part in the development of carcinoma cannot, in view of present knowledge be denied. The consensus at present seems to favor their being essentially tumors and not, as they were previously considered hyperplasias of the mucous membrane. It is undeniable that many cases which after microscopic study have been diagnosed as simple, benign papillomas of the renal pelvis, ureter or bladder have subsequently developed as cases of carcinoma. Again, undoubted carcinoma has been found in the renal pelvis with typical benign papilloma in the ureter as well as in the kidney pelvis. It is such histologic and clinical considerations that have recently led so many authorities, Kummel included, to take the

14 Zironi, G. Cancer primitif de l'uretère droit. *Ann d mal d org gen-urin* **27** 81, 1909

15 Metcalf, W. F., and Safford, H. E. A Case of Carcinoma of the Ureter, *Am J M Sc* **129** 50, 1905

16 Davy, R. Clinical Lecture on Excision of Left Kidney, *Brit M J* **2** 757, 1884

17 Stewart, R. L. Primary Tumors of the Ureter, *Brit J Surg* **13** 667, 1925-1926

18 Le Dentu, A. *Ann d mal d org gen-urin* **17** 955, 1899

19 Leone, P. Tumori sperimentali del rene e dell'uretère da catrame. *Arch ed atti Soc ital di chir* **34** 111, 1927-1928

rather radical point of view that every papillary proliferation of the mucous membrane of the renal pelvis or of the ureter is a malignant tumor. Undoubtedly, this point of view is the safest so far as the future of the patient is concerned.

Pathology—A survey of the histology in the cases of primary ureteral tumors reported suggests the following simple classification:

Epithelial tumors

Simple or benign papilloma

Malignant papilloma (papillary carcinoma or papillary epithelioma)

Nonpapillary carcinoma or epithelioma (simple, squamous, adenomatous)

Connective tissue tumors

Sarcoma

Myosarcoma

Simple or Benign Papilloma The type of ureteral tumor most frequently met with by far is that of the simple or benign papilloma. It may occur singly, as groups of multiple tumors or as a generalized papillomatosis affecting much of the ureter. It possibly shows a predilection for either the upper or the lower end of the organ, and occasionally occurs at each extremity, as in Le Dentu's case. It may be sessile or pedunculated, at times markedly so, as in Culver's²⁰ case in which the tumor consisted of a mass 3 cm long attached to the ureteral mucosa by a narrow pedicle. Occurring in the lower portion of the ureter, it may extrude through the ureteric orifice, as noted by Kraft²¹ and others.

Histologically, the ureteral papilloma is no different from that encountered in the bladder or renal pelvis. Essentially, it consists of branching, poorly cellular, vascular, connective tissue cores or stalks surmounted by multiple layers of well differentiated epithelial cells occurring in a variable number of layers, the whole giving rise to a villous or papilla-like arrangement. The individual epithelial cells are rather uniform in size, regular, symmetrical and usually attached at right angles to the cellular stalk. The cells do not appear to infiltrate the connective tissue stalk at their points of origin, but here and there aggregates of small round cells, probably a manifestation of irritation, may be noted. Whether broad-based or pedunculated, the tumor shows no tendency to infiltration or invasion at the point of attachment.

Malignant Papilloma This group comprises those tumors classified as papillary carcinoma and papillary epithelioma, and includes neoplasms of varying degrees of malignancy. Almost invariably, the malignant papilloma occurs singly and appears to have a predilection for the lower

²⁰ Culver, H. Papilloma of the Ureter, *J Urol* **6** 331, 1921.

²¹ Kraft, S. Primary and Secondary Ureteral Papillomas, *Ztschr f urol Chir* **16** 385, 1922.

part of the ureter. Macroscopically it differs but little from the so-called benign papilloma. Microscopically, it may manifest varying stigmas of malignancy with a gradual transition from nonmalignant to malignant features such as to necessitate the most careful histologic study for accurate diagnosis as emphasized by Richter, Kummel, Glas²² and others. In some cases only early signs of local malignancy, such as increased proliferation of slightly atypical cells with a loss of basal cell polarity, are noted. In others, there is much infiltration at the point of attachment, even to such an extent as to be observable macroscopically. The individual cells in the more malignant types are heaped up in thick layers, many showing marked polymorphism with large and small cells occurring in disorderly, disarranged masses. Most important is the tendency of these cells to infiltrate at their points of origin the stalks or cores or the connective tissue substance of the stalks. Mitosis in varying degrees is usually prominent. Destructive infiltration of the ureteral wall and invasion of periureteral tissue occurs in the pronouncedly malignant types.

Nonpapillary carcinoma. This group comprises the more uncommon forms of epithelial tumors of the ureter such as those classified variously and at times bizarrely as "medullary," "encephaloid," "columnar," "adenomatous," "cylindric," "transitional celled," etc. In this group may be placed the squamous cell tumors and tumors of frank ectodermal derivation. Generally speaking, ureteral tumors of this group are the most malignant and show the earliest and most extensive metastasis. Histologically, their recognition is comparatively simple the stigmas of malignancy being unmistakable and papillary or villous formation being absent or at best simply suggested in the general arrangement of the tumor masses. That at least some of the morphologic and histologic characters presented by these tumors may originate from simple papillomas seems proved by Leone's experimental demonstration of the progressive evolution of neoplastic epithelial processes from simple papillomas to squamous cell, papillary and even alveolar carcinomas.

Connective Tissue Tumors. These tumors, of no special interest in this report, but mentioned for the sake of completeness, are extremely rare. Stewart and Kummel agreed that only five have been reported. One, Ribbert's case, is classed as a myosarcoma. cursory examination of the reports leads us to believe that in most of the cases, possibly all, the ureter was only secondarily invaded by the sarcomatous growth.

Malignancy and Metastasis.—As previously indicated, there is much confusion regarding the exact position that must be assigned to the so-called benign papillomas of the urinary tract as regards malignancy

²² Glas, R. Primary and Metastatic Cancer of Ureter. *Wien klin Wchnschr* 39 1145, 1926.

The consensus of latter day investigators, as stressed especially by Dózsa, appears to be that benign papillomas of the urinary tract, if such there are, are extremely rare and that in most, if not all, such tumors careful histologic examination will show malignancy, although at times early. Undoubtedly, the clinical course of most of the tumors diagnosed as simple papillomatous tumors supports this view, extreme though it may appear. Glas and Player²³ asserted and emphasized that the metastasis from a so-called simple papilloma may exhibit all the signs of malignancy. Janssen,²⁴ among others, believed that papillomas of the urinary tract do not extend until lesions of the mucosa, inflicted by instrumentation or otherwise occur. This view of extension of the so-called simple papillomas by engrafting is rather fully expressed by many authors and certainly is strongly suggested by such cases as Vorpahl's,²⁵ Spiess²⁶ and Walker's,²⁷ among others. Some authorities assert that in contradistinction, the most malignant and especially the nonpapillary types of tumor extend by means of the lymphatics. A summary of the pathologic observations in the reported cases does not give much information concerning metastasis, and the assumption of a lymphatic route for metastasis, while undoubtedly generally correct, must be accepted as an "*a priori*" one. Extension of tumor growths in the cases in which it was noted was along the ureter or the periueteral tissues. In Glas' case, the extension involved the tissues surrounding the opposite ureter. Metastasis to the liver is mentioned seven times, metastasis to the lungs five times, metastasis to the lymph glands eight times. Involvement of the vertebra occurred once and of the spleen once.

Although we cannot as yet subscribe to the radical view that all papillomatous growths found in the ureter are malignant, we hold that they must be viewed with suspicion and subjected to a most thorough histologic study. We believe that the general histologic picture in the papillary types of tumors is relatively unimportant and that most careful and painstaking search should be made for atypical cells, atypical cell arrangement and cell invasion, with proper evaluation of these, before a satisfying conclusion can be reached as to the exact nature of such tumors. This will undoubtedly lead to the recognition of malignancy.

23 Player, L. F. Primary Ureteral Carcinoma, with Case Report and a Review of the Literature, *Urol & Cutan Rev* **32** 438, 1929.

24 Janssen, P. Aussergewöhnliche Tumorbefunde den oberen Abschnitten der Harnwege, *Ztschr f urol Chir* **9** 474, 1922.

25 Vorpahl, K. U. F. Primary Carcinoma of the Ureter, *Am J Urol* **2** 509, 1905.

26 Spiess, P. Die primären epithelialen Tumoren des Nierenbeckens und des Ureters, *Centralbl f allg Path u path Anat* **26** 553, 1915.

27 Walker, J. W. T. *Proc Roy Soc Med (Sect Urol)* **14** 42, 1921.

per se in many growths that would otherwise be classified as benign and will lessen observation of metastasis from tumors apparently benign. That the so-called simple papillomas may at times evolve into tumors of entirely different character is certainly at least suggested by clinical and experimental data.

SUMMARY

A case of primary carcinoma of the ureter is reported, with a résumé of the salient features of the forty-eight cases recorded in medical literature. Twenty-eight of the recorded tumors were papillary, twenty were nonpapillary. The incidence is about equal for both sexes, with the greatest number occurring during the sixth and seventh decades of life. The lower part of the ureter is more frequently the site of the lesion. No etiology can be ascribed, although concurrent lithiasis was present in six cases. The consensus seems to be that so-called benign papillomas of the ureter and of other parts of the urinary tract must always be regarded as highly suspicious growths so far as actual, as well as potential malignancy is concerned.

TESTICULAR TUBULAR ADENOMA OF THE OVARY

ITS ETIOLOGIC RELATION TO EMBRYONIC VESTIGES AND SPONTANEOUS SEX REVERSAL OF THE FEMALE GONADS

REPORT OF A CASE^{*}

NICHOLAS W. POPOFF, M.D.

ROCHESTER, N. Y.

The subject discussed here concerns one of the rarest tumors encountered in the ovary. Although this growth supposedly belongs to the group of nonteratoid tumors, its structure, its origin and its possible relation to hermaphroditism involve the general question of embryogenesis of the sex glands. It was Pick¹ who first described in 1905, an unusual tubular adenoma of the ovary and designated it as adenoma tubulare ovarii testiculare. Since that time a few additional cases of similar tumors have been reported and live discussion of these tumors was brought up in recent years by Meyer,² Neumann³ and Heesch.⁴

Two points are essential in discussion of this pathology: 1. Do these tumors originate from the female or male germinal anlage, and if so, do they arise from differentiated sex cells or do they spring from undifferentiated sexual primordial elements that may or may not have any faculties toward sexual differentiation? 2. Should the presence of adenoma tubulare ovarii testiculare be considered as equivalent to hermaphroditism and interpreted as the result of prenatal misbuilding

^{*} Submitted for publication, Sept. 9, 1929.

^{*} From the Department of Laboratories, Highland Hospital.

1. Pick, L. Ueber Adenome der mannlichen und weiblichen Keimdruse bei Hermaphroditismus verus und spurius, Berl. klin. Wchnschr. **17** 502, 1905.

2. Meyer, R. Drei Beitrage zur Kenntnis seltenerer Ovarialtumoren, Arch. f. Gynak. **109** 212, 1918, Ueber einen Fall von doppelseitigen Ovotestis beim Neugeborenen sowie uber besondere Formen der Keimdrusen-Geschwulstbildung bei Pseudohermaphroditismus und Hermaphroditismus verus sowie uber gleichartige Geschwulste bei nichtzwitterigen Personen, *ibid.* **123** 675, 1925.

3. Neumann, H. O. Das tubulare Adenom des Ovarium und seine Beziehungen zum Hermaphroditismus verus, Arch. f. Gynak. **126** 553, 1925, Das Adenoma tubulare testiculare Ovotestis, Virchows Arch. f. path. Anat. **270** 501, 1928, Analoge Keimepithelblastome der Hoden und der Ovarien sowie ihr Vorkommen beim menschlichen Zwitter oder Scheinzwitter, Arch. f. Gynak. **131** 477, 1927.

4. Heesch, O. Zur Kritik der tubularen Ovarialadenome, Virchows Arch. f. path. Anat. **268** 280, 1928.

of the gonads, or should it be attributed to postnatal changes of the gonads and discussed in the light of present knowledge of sex reversal and intersexuality of the gonads?

These two questions are not easy to answer especially in the case of the highest mammal (adult man). The questions of pathologic diagnosis and terminology present, also, great difficulties, if one may judge from the difference in opinion of the pathologists whom I have consulted on this case. One who favors and follows Pick's conception of the existence in the parenchyma of the ovary of tubular testicular anlage material has no difficulty in interpreting both the nature of this ovarian tumor and its relation to hermaphroditism. However, the presence of a differentiated tubular testicular anlage in the ovaries may be justly doubted, while the existence in the ovary of a true masculine homologue in the form of rete and tubuli recti may be accepted and these may be suggested as a possible source of this growth. Since there are two different opinions regarding the origin of the rete ovarii the followers of the wolffian origin and the followers of the genital or germinal origin of the rete may tag these tumors accordingly. Ewing's⁵ forceful defense of the teratoid origin for embryonal alveolar and diffuse carcinomas of the testicle and L'Esperance's⁶ for embryonal carcinomas of the ovary may suggest the interpretation of the tumor under discussion as a one-sidedly developed teratoma. Still if one is not inclined to go into details of the embryonic genesis of these tumors, he may simplify the whole matter by calling them simply hamartoma tubulare in the sense of Albrecht.

In pathologic discussion of these tumors the embryologic and experimental data concerning gonads must be considered as it is undeniable that the rudimentary state of the sex glands and cellular deviations or cellular misbuilding, without formation of organoid tumors is often met among cases of this type. A clinical course with considerable local destruction and but little tendency toward metastasis is rather characteristic of these tumors and this puts them into a specific group of ovarian neoplasms. The observed sexual deviations toward hermaphroditism, intersexuality and gynandromorphism, the changes in the menstrual cycle and the undeniable hormonal influence of these tumors on the remaining ovary and the body generally, necessitate special attention from the clinical point of view. The case in question bears also certain peculiar clinical and morphologic features that are of considerable interest.

5 Ewing, J. Teratoma Testis and Its Derivatives, Surg. Gynec. Obst. **12** 230, 1911.

6 L'Esperance, E. S. Embryonal Carcinoma of the Ovary, Arch. Path. **5** 402, 1928.

REPORT OF CASE

A patient, aged 31, was admitted to the hospital on Sept 27, 1925, with the following history

She was married in February, 1922, and the first child was born in February, 1923. She nursed the infant for nine or ten months. Her menstrual function was fully reestablished in August, 1923, or about seven months after childbirth. She continued to menstruate regularly every twenty-eight days until February, 1924. She did not menstruate in March, but did not consider herself pregnant. The menstruation in April was perfectly normal without any unusual manifestation. She did not menstruate again until September, 1925, then she had a slight flow described as spotting. About six months previous to admission to the hospital, she was examined by Dr. W. B. Conner, who detected a movable tumor in the right quadrant of the pelvis. She was examined at intervals of one or two months without any apparent change being found in the size of the tumor.

On admission to the hospital, she appeared to be well developed and well nourished, generally robust and absolutely feminine. No anatomic abnormalities or defects were found. No evidence of sexual or psychic deviations was obtained from her past history or on physical examination. The family history in regard to congenital malformations, constitutional diseases or occurrence of twins was negative. Her first menstruation began at the age of 14, lasted on an average three days and remained always regular, moderate in amount and painless. No thyroid disorders were noted, and on admission the thyroid appeared normal. The breasts were quiescent with no signs of lacteal secretion. The heart and lungs were normal. The abdomen moved evenly with respiration. It was well covered with subcutaneous fat. No abnormalities in the distribution of the hair around the external genitalia and on the face were noted. The external genitalia appeared free from any pathologic changes of note. On palpation of the abdomen, no tenderness was elicited. Vaginal examination revealed the presence on the right side of a tumor that was freely movable and apparently not attached to the uterus. On account of its smoothness and density, a tentative diagnosis of solid tumor of the ovary was made. The laboratory observations, including the results of examination of the urine and blood and of the Wassermann test, were essentially negative.

On September 28, or six months after the detection of the tumor, the operation was performed, and a large solid tumor of the right ovary was removed. The tumor was encapsulated and there was no evidence of the tumor breaking through the capsule, nor was there any enlargement of the lymph nodes in the pelvic region. The other abdominal organs were normal. The left ovary was normal and appeared quiescent. The appendix was somewhat congested and for this reason was removed at operation. The abdomen was closed without drainage, and the operation was followed by a complete and uneventful recovery.

Gross Examination of Tumor—On pathologic examination, the tissue received had the appearance of a pear-shaped, smooth, solid tumor measuring 8 by 6 cm. The attached ovary was flattened and compressed, and the hilar portion of it was fused with the tumor, which appeared to begin near the medullary portion of the hilar region of the ovary. The cut surface showed a solid, edematous, pinkish tumor, rather uniform in structure, well encapsulated and without evidence of degeneration, hemorrhages or cystic formations. While the central portions were harder and resembled somewhat soft fibroma or xanthoma, the subcapsular portions were more delicate and homogeneous. The cut surface of the ovarian portion was free from any evidence of recently formed or involuting corpora lutea, and

no fresh hemorrhages were noted. No follicular cysts were present, and the cortical portion of the ovary appeared uniformly fibrotic and free from any gross evidence of functional activity.

Microscopic Examination—On microscopic examination, the sections had a varying appearance, depending on the portion of the tumor from which they were cut. The ovarian portion showed a smooth cortex, covered on the outer surface with high cuboidal, quiescent, germinal epithelium occasionally showing short abortive invaginations. Beneath it was seen a fibrous tunica albuginea that was poor in cells. The outer layer of the cortex contained only a few primordial follicles with occasional oocytes. In no place was a ripe follicle found. The primordial follicles revealed all the signs of degeneration, manifested by cicatrization and complete absence of follicular cystic degeneration. The theca interna was furnished with a single layer of low cuboidal epithelium but neither the elements of the theca interna nor those of the theca externa showed transformation into lutein cells. A number of rather large corpora albicantia were seen, but no microscopic evidence of recent hemorrhages, hemochromatosis or unusual histiocytic activity was present. The medullary portion of the ovary consisted of loose connective tissue well supplied with blood vessels and lymphatics. Amid the stroma cells of the medullary portion were seen conspicuous small groups and islets of large, irregular, polygonal cells structurally corresponding to the paraganglionic cells or paraganglionic tissue described by Berger,⁷ Wallart,⁸ Winawarter⁹ and others. In no way were these cellular inclusions related to the tumor growth. Neither tubular wolffian relics nor rete tubules were found. Just on the outer border of the hilum was seen a well defined margin of an epithelial tumor growth delimited on its outer surface not with the regular thick capsule but with only loose connective tissue furnished by the stroma of the hilum itself (fig 1 *Hro*). The architecture of the growth on the whole, was that of an organoid tubular type and was represented by sheaths and groups of cells which formed solid strands, cylindric cords and tubules with an occasional axial lumen and surrounded by delicate partitions of connective tissue (fig 1 *Esc Crd*, *Tbl*, *Pit*). Some of the tubules appeared well differentiated and some were lined with high cuboidal epithelium and supplied with true basement membrane (fig 2 *Bm*). The cells of the tumor were uniform in size with round or oval nuclei which contained one, and occasionally two, rather prominent nucleoli. The nuclear chromatin was arranged mostly in loose spirem, and only occasional mitoses were seen. The cytoplasm was indistinct, no clearly visible intercellular borders were seen, and the axial fusion of the cytoplasm gave in some places the appearance of syncytium-like structures. Nowhere were foci of necrosis, massive degeneration or perivascular arrangement found.

Among the cords and tubes, and intimately related to them were seen strikingly different structures composed of large, clear, acidophilic cells. These clear cells were arranged mostly in groups, islets and voluminous masses, some of which even appeared like tubes, with axial lumen and basement membrane (fig 3 *Fic*). These cells varied in size, some reaching a diameter of 40 microns. They con-

7 Berger, L. La glande sympathicotrope du hile de l'ovaire humain, Arch d'anat d'histol et d'embryol **2** 259, 1923.

8 Wallart, J. Sur le tissu paraganglionnaire de l'ovaire humain, Arch d'anat d'histol et d'embryol **7** 3, 1927.

9 Winawarter, H. A propos des cellules sympathicotropes de l'ovaire humain, Compt rend Soc de biol **89** 830, 1923. L'appareil phochromique de l'ovaire humain, Bull d'histol appliq a la physiol **1** 145, 1924.

tained oval or round nuclei which appeared rather small in relation to the voluminous size of their cytoplasm. The most unusual feature of the nuclei was their polychromaticity. While some of the nuclei appeared vesicular and were clearly and lightly stained, the chromatin granules of others appeared coarse and the karyoplasm was stained deeply—almost black—so that no nuclear details could be recognized (fig 3). The lightly stained nuclei showed a clearly visible nuclear membrane and usually one prominent nucleolus. These clear cells stood out conspicuously on account of their large size and the eosinophilic staining of their cytoplasm. In the cytoplasm of these large cells it was easy to see the dense perinuclear zone, not sharply delimited and deprived of vacuoles (fig 3 *Dps*), and the external zone having a clear aspect with vacuoles separated by thin cytoplasmic strands (fig 3 *Cvcz*). In the sections fixed in formaldehyde and stained with sudan III, these cellular inclusions were stained in orange red, proving thus their fatty nature. These clear acidophilic or fat-laden cells resembled more closely the interstitial cells, namely, those interstitial cells which originate in the embryonal ovary and testis among the medullary or sexual cords and which are formed from the epithelial elements of the cords undergoing a regressive process and fatty degeneration. In examining serial sections, it is hardly possible to confuse these clear cells with true lutein cells or the interstitial cells of Leydig. During the process of organoid transformation, the individual epithelial elements undergo rather characteristic changes manifested by gradual hypertrophy of the cytoplasm, increase in size and number of the granules and vacuoles (figs 3 and 4), loss of intercellular boundaries and final transformation into huge, formless masses with nuclei stained black, gathered together and pushed to one side (fig 5). This regressive metaplasia of the epithelial elements takes place slowly and is evidently determined to some extent by the process of vascularization. Wherever the capillaries penetrate into the structures and come into contact with the epithelial spherules, the latter begin to show gradual degeneration with accumulation of fat and final transformation into the structureless masses described (figs 3 and 4 *Bc*). There was no evidence of degeneration of the connective tissue stroma or of histiocytic and lymphoid infiltration. The appearance of the large, clear, fat-laden cells suggests the local fatty degeneration of the epithelial ingredients of the cords and not a fatty infiltration that determines the formation of mesenchymal ovarian lutein cells and the cells of Leydig.

The main bulk of the tumor was composed mostly of solid cords, tubes and irregularly arranged and closely packed epithelial cells forming a syncytium which may be regarded as the primordium of a Sertoli cell syncytium. The cords of the tumor were undoubtedly homologous to the medullary or sexual cords of the first proliferation and in the process of evolution showed transformation into tubules closely resembling young seminiferous tubules, but no nuclear changes indicative of further differentiation and the formation of spermatogonia were found in any section. The stroma of the tumor participated actively in the growth, and its distribution and relation to the epithelial anlage of the tumor suggest an unmistakable tendency toward dissociation of the cords, and this phenomenon may mean the initial step toward organogenesis. In the sections from the denser portion of the growth, the microscopic picture presented certain peculiarities deserving of special consideration. Here the epithelial cells appeared small and grouped together in masses, strands and sheaths without any definite organoid arrangement. The marginal portions of these sheaths showed gradual dedifferentiation and their cellular boundaries faded into surrounding cellular fibrous tissue. The latter appeared loose, edematous and free from lymphoid and histiocytic infiltration, and no such inclusions as muscle, cartilage or derivatives of the entoderm or ectoderm were found.

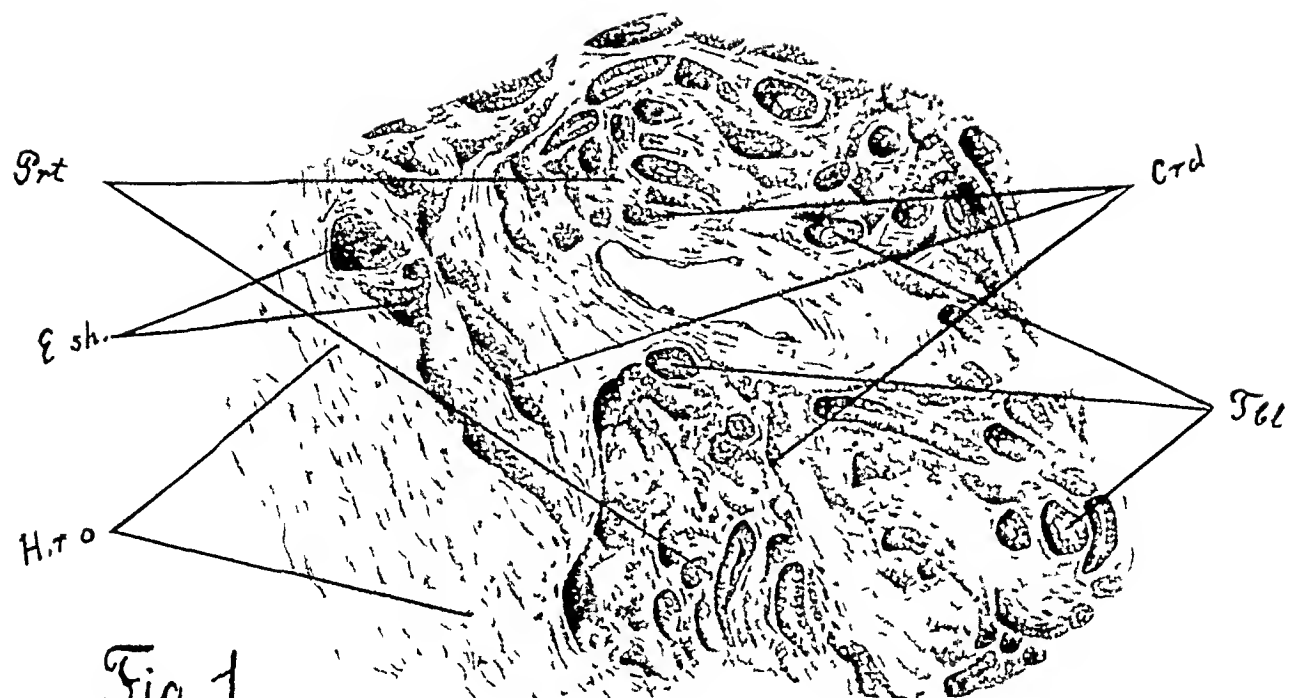


Fig 1.

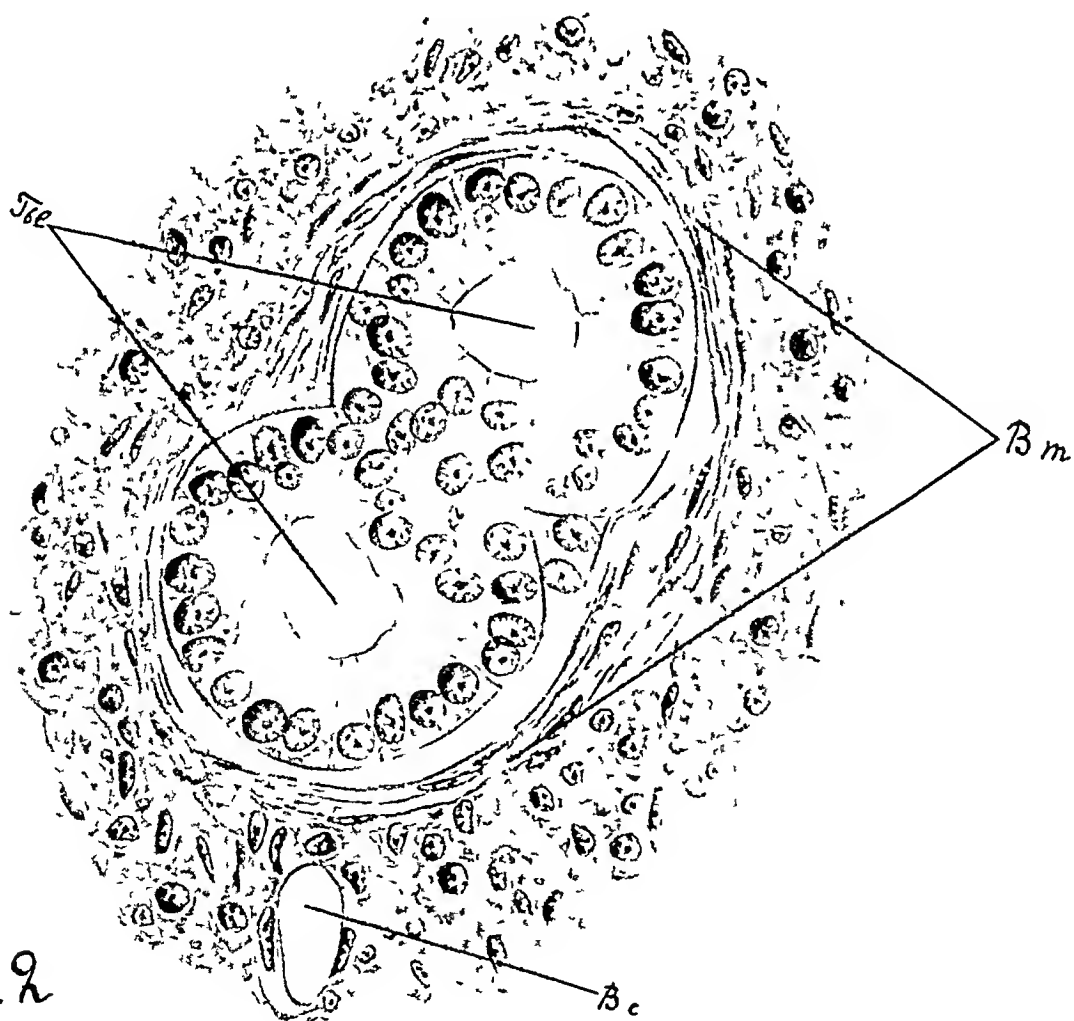


Fig. 2

EXPLANATION OF FIGURES

All drawings were made with the aid of a camera lucida of Abbe figure 1, with Bausch and Lomb 16 mm objective, 10 ocular and tube half drawn, figures 2, 3, 4 and 5 with 4 mm objective, 10 ocular and tube completely drawn

Fig 1—Low magnification of a section of the tumor cut through the place of its attachment to the hilar region of the ovary (*H i o*) The tumor growth is shown to consist of epithelial sheaths (*E sh*), cords (*C i d*) and tubules (*T b l*) with delicate connective tissue partitions (*P i t*)

Fig 2—Well formed tubes are seen, with axial lumen lined with a single layer of epithelium (*T b l*) and furnished with a basement membrane (*B m*)

Fig 3—Distinct organoid tubular structures appear here, the epithelial constituents of which undergo gradual hypertrophy and fatty degeneration with transformation into large, clear, fat-laden cells (*F l c*) forming islets and huge rosetts Nuclear polychromaticity of the cells and deep staining of the karyoplasm are characteristic of these cells The dense perinuclear zone (*D p z*) and the clear vacuolar external zone (*C v e z*) are conspicuous Blood capillaries (*B c*) with their relation to *F l c* are shown

Fig 4—A further step in the hypertrophy and degeneration of the epithelial formations, with an increase in the size of the granules, vacuoles and loss of intercellular boundaries

Fig 5—The final stage in the degeneration, with transformation of the epithelial formations into huge, formless masses, the nuclei of which are stained black, gathered together and pushed to one side and the cytoplasms completely fused

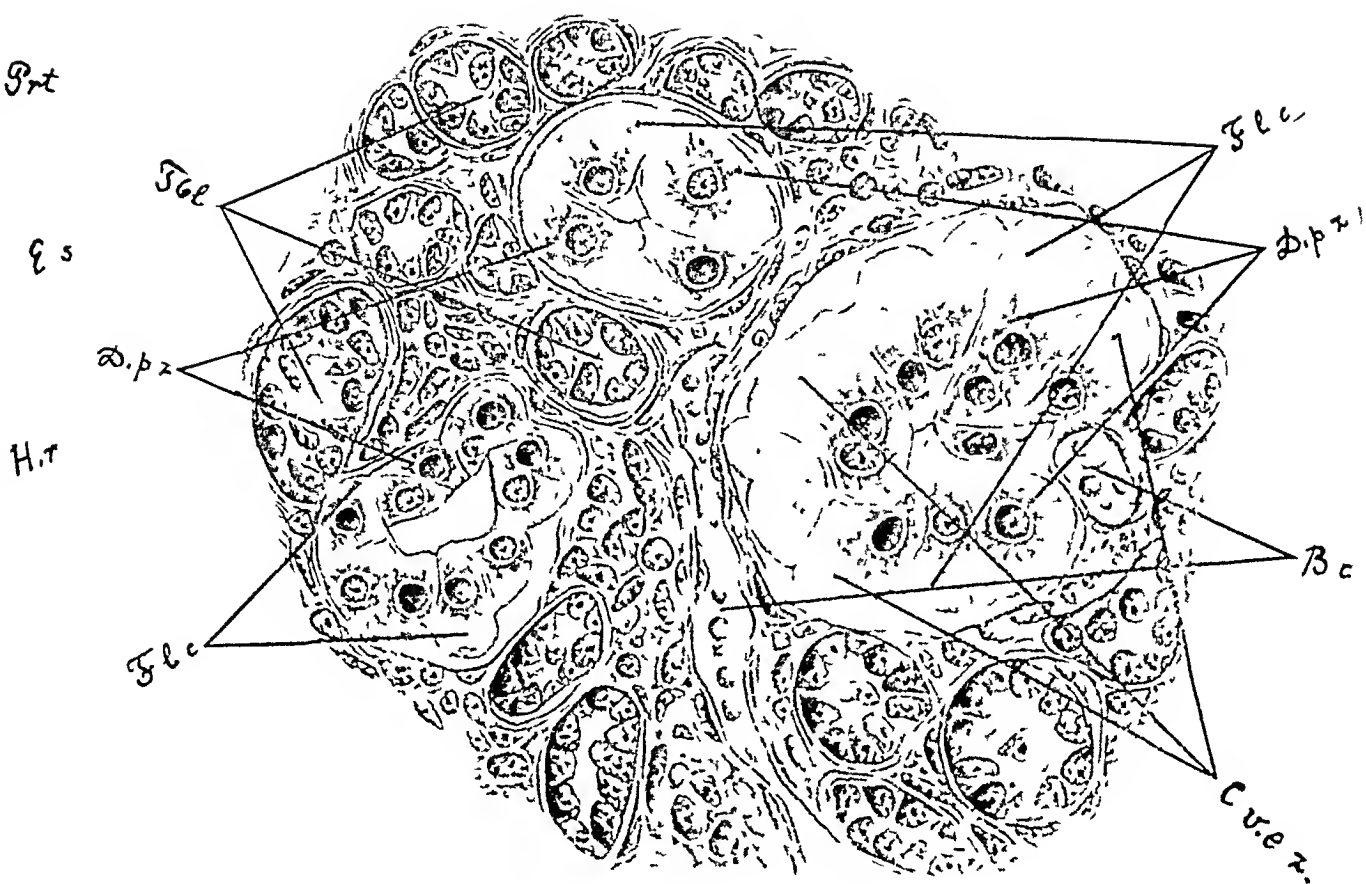


Fig. 3

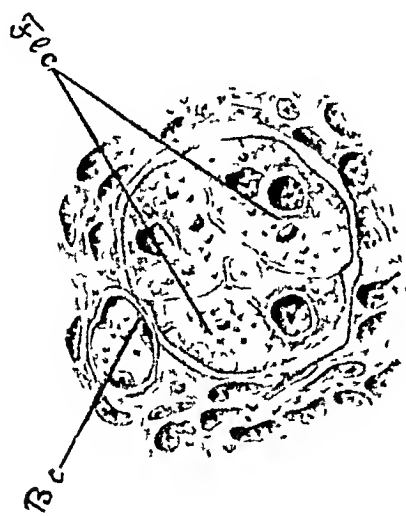


Fig. 4

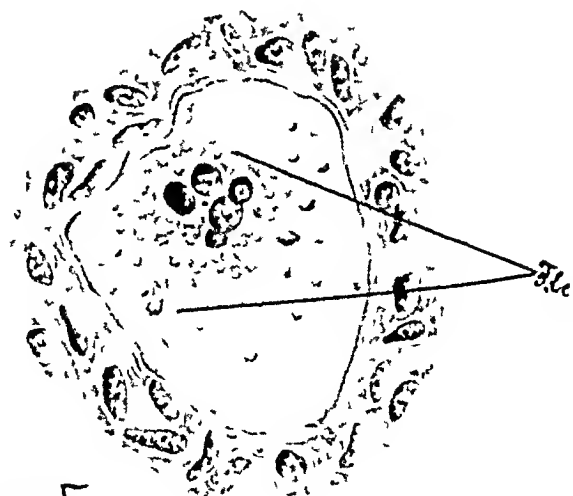


Fig. 5

COMMENT

The described picture is unusual enough to make the question of diagnosis a subject of considerable disagreement. By virtue of the embryologic complexity of the ovary certain tumors, and especially those arising in the hilum, will remain for a long time a matter of individual interpretation, which may be based either on pure embryologic data or on the general cellular appearance and clinical behavior. The nature of the tumor discussed cannot be understood without embryologic consideration, and its diagnosis can be settled only by the method of exclusion.

Here, in the region of the hilum and mesovarium, are found in the fetal life various complicated formations undergoing specific evolution and involution and thus affording every chance for different anomalies. Four of these embryologic formations which deserve chief consideration are paroophoron, epoophoron, rete and the medullary cords of the first proliferation. Each of these ovarian inclusions has, in fetal life, its own developmental cycle, although they all remain unused in the final formation of the ovary. This fact offers an understandable source of various ovarian anomalies and pathologic conditions manifested by incomplete regressions of the aforementioned embryonic constituents of the fetal ovary, their misplacement and the pathologic formation of cysts, adenomas and carcinomas.

It is generally agreed now that paroophoron and epoophoron are of wolffian origin. The fates of these two wolffian derivatives are somewhat different. While the epoophoron shows until birth progressive evolution, the paroophoron undergoes regression soon, although it does not disappear entirely at the time of birth and during the first days of extrafetal life. The rapid involution of the latter accounts for the rarity of the paroophoric anomalies. Winiwarter¹⁰ observed besides paroophoric cyst formation an interesting anomaly, in a six months' ovary, of the nature of a true epithelial tumor somewhat resembling carcinoma. Anomalies of the epoophoron are more common, being manifested by simple enlargement of the tubules, their sacculation, the formation of simple and papillary cysts and diffuse proliferation of the epithelial lining with all the characteristics of malignant carcinomatous growth. These wolffian relics may present themselves either in the form of spheric, trabecular or compact epithelial collections resembling malpighian cells or in the form of tubes or cysts lined with cuboidal,

10 Winiwarter, H., and Sanmont, G. Nouvelles recherches sur l'ovogenese et l'organogenese de l'ovaire des mammiferes (chat), Arch de biol **24** 373, 1909, La constitution et l'involution du corps de Wolff et le developpement du canal de Muller dans l'espece humaine, Arch de biol **25** 169, 1910

cylindric and often ciliated epithelium. According to Masson,¹¹ in addition to the various types of cysts these embryonal vestiges may give origin to massive wolffian epitheliomas which may run the course of true carcinomas with lymph node involvement and generalization. In my case, in which no signs of cysts, or even microcysts, were found, the massive wolffian epithelioma only may be considered. Here I have to state what constitutes the wolffian epithelioma and what are the main histologic and clinical features of the so-called wolffian epithelioma.

From the descriptions of cases designated as cases of wolffian epithelioma (Delannoy and Breton,¹² Leveuf and Heraux,¹³ Corsy and Montpellier¹⁴) one gets the information that grossly, in the early stage these tumors appear regular, round, sometimes pear-shaped and encapsulated. The cut surface is grayish or reddish with a marble-like appearance. Histologically they are composed of epithelial cellular nests, strands, papillary arborescences and tubes lined with cuboidal or cylindric cells which are irregular in volume, contain basal nuclei and show intense chromatophilia, nuclear monstrosities and numerous mitoses. The stroma is rather vascular, myxomatous or dense and without collagen, and in its distribution and growth it does not show any tendency toward dissociation of the adjacent epithelium, a phenomenon that is observed in embryonal ovarian tumors arising from the germinal epithelium of the first proliferation (Peyron¹⁵). In some cases, the remnants of the ovary can be seen; in others, no remnants of the normal ovary are found. No preexisting Leydig's "Zwischenzellen" or interstitial cells of Turner are found and no evidence of the transformation of the epithelial elements into clear or fat-laden cells is present and no Call-Exner bodies are formed. From the clinical point of view, no precocious virilism, sex changes, hirsuties or menstrual disturbances are associated with these wolffian tumors.

Comparing the structural features of my case with the description given of solid wolffian epitheliomas, one is left without justification for calling the tumor in question mesonephroma, a term too vague and

11 Masson, P. Essai sur les tumeurs non-teratoides de l'ovaire, Gynec et Obst 6 81, 1922.

12 Delannoy, E. and Breton, A. Un cas d'épithélioma Wolffien de l'ovaire, Bull Soc d'obst et de gynec 4 239, 1926.

13 Leveuf and Heraux. Un cas d'épithélioma Wolffien de l'ovaire chez une fillette de sept ans, Ann d'anat path 3 639, 1926.

14 Corsy, F., and Montpellier, J. Sur les évolutions cellulaires le diagnostic histologique et les homologues des épithéliomes ovariens issus de vestiges Wolffiens, Bull de l'Assoc franç p l'étude du cancer 16 537, 1927.

15 Peyron, A. Sur les caractères et les tendances évolutive d'un type de tumeur ovarienne issu des cordons médullaires, Compt rend Soc de biol 90 575, 1924.

groundless to apply. It is true that in spite of the epithelial lining resembling the wolffian lining certain types of tumors with rare regular lumina are difficult of diagnosis and can be attributed to medullary cords (Corsy-Montpellier¹⁴), but in my case there are other, more important features that speak against the diagnosis of mesonephroma. The transformation of epithelial formations into diffuse mesenchymal sheaths may resemble the structure of a mixed tumor of the kidney, but the other dominant characteristics of the growth in question could not be fitted to Wilm's congenital tumor, especially in a case like mine, in which the primary ovarian origin of the tumor is unquestioned.

The discussion of ovarian mesonephromas brings immediately the question of rete ovarii and its relation to ovarian neoplasms. Conflicting embryologic data in regard to the origin and fate of the rete ovarii leave the pathologist without true guidance in identifying, classifying and interpreting ovarian tumors arising from the rete. Under the term "rete," I understand the epithelial formations seated in the hilum of the ovary and extending into the mesovarium on one side and into the medullary substance on the other side. They present themselves in the form of solid epithelial buds and sometimes in the form of ramifying canals lined with cuboidal—or more seldom with cylindric—epithelium, are furnished with a delicate basement membrane and sometimes have smooth muscles around. For the reason that these epithelial formations are in relation by continuity or by contiguity on one side to the medullary cords and on the other side to the epoophoric tubes, two different opinions regarding their origin are offered.

According to Mihákovics,¹⁶ Sainmont,¹⁷ Winwarter,¹⁸ Balfour¹⁹ and Wallart,²⁰ rete ovarii is homologous to rete testis and is of wolffian origin, while the seminiferous tubes are homologous to the medullary cords of the ovary and are derivatives of the germinal epithelium. According to Allen,²¹ Meyer,²² Felix,²³ Kingsbury²⁴ and Wilson²⁵ the

16 Mihákovics, V. Untersuchungen über die Entwicklung des Harn- und Geschlechtsapparates der Amnioten, *Internat Monatschr f Anat u Physiol* **2** 41 1885

17 Sainmont, G. Recherches relative à l'organogenese du testicule et de l'ovaire chez le chat, *Arch de biol* **22** 71, 1906

18 Winwarter (footnote 10, second reference)

19 Balfour, F. M. On the Structure and Development of the Vertebrate Ovary, *Quart J Mic Sc* **18** 383, 1878

20 Wallart, J. Contribution à l'étude des origines du rete ovarii, *Bull d'histol appliq à la physiol* **5** 181, 1928

21 Allen, B. M. The Embryonic Development of the Ovary and Testis of the Mammals, *Am J Anat* **3** 89, 1904

22 Meyer, R. Zur Kenntnis der kranialen und kaudalen Reste des Wolff'schen (Gartner'schen) Gänge beim Weibe, *Centralbl f Gynak* **7** 203, 1907

rete ovarii is of germinal celomic origin and the observed communication between the rete and epoophoric tubes is considered by advocates of the germinal theory as accidental. Wallart's²⁰ case of ovarian aplasia in which gradual and uninterrupted evolution of the epoophoric tubes into branchings characteristic of rete could be positively traced, seems to corroborate the fundamental studies of Sammont and Winiwarter and at least brings new evidence for the wolffian origin of the rete.

The rete ovarii is well developed in the fetus and in the new-born infant, but in adults it is almost always found in more or less rudimentary form. In certain periods of life, for example in gestation, its lining epithelium becomes high cylindric and sometimes is furnished with a border of vibrating cilia. According to Winiwarter¹⁰ the anomalies derived from the rete are as a rule more common than those from the epoophoron and they appear in the second half of gestation and tend to affect the mesovarian and intra-ovarian portions more often than the epoophoric portion. Cystic papillomatous cavitations, cystic tubes and voluminous postnatal cysts are the main pathologic abnormalities of rete origin. Winiwarter believed that rete cysts, developing toward the end of gestation, are influenced by interstitial tissue. His observations on the interrelation between developmental growth of the rete and the apparition of interstitial cells on one side and the developmental arrest of the rete shortly after birth with degeneration of the mesovarian interstitial cells on the other side is of great significance. He attributed this phenomenon to the trophic influence of the interstitial tissue, but in the light of the latest work on ovarian grafts, x-ray action on the young ovary and free-martin intersexuality his observations may be interpreted by the advocates of the germinal origin of the rete differently and with conclusions casting doubt on the extragenital origin of the rete. This brings us to the discussion of the fourth last and most important constituent of the fetal ovary, namely medullary cords, the anomalies of which have immediate bearing on the origin of the tumor in question.

The germinal origin of the medullary cords is definitely established and generally accepted. During the development of the gonads, the germinal epithelium gives, according to Winiwarter and Sammont, three successive proliferations, each characterized by its particular evolution. At the early stage, the stage of indifferent sexuality the first prolifera-

23 Felix, W. The Development of the Urmogenital Organs. Manual of Human Embryology, F. Keibel and F. Mall, Philadelphia J. B. Lippincott Company, 1912, vol. 2, p. 752.

24 Kingsbury, B. F. The Morphogenesis of the Mammalian Ovary. Felix Domestica, Am. J. Anat. **15** 345, 1913.

25 Wilson, K. M. Origin and Development of the Rete Ovarii and the Rete Testis in the Human Embryo, Contrib. Embryol. **17** 69, 1926.

tion of the germinal epithelium gives rise, by invagination, to thick, plain, cellular cords, ramifying and anastomosing and encroaching on subjacent connective tissue. After they break their relation with the germinal epithelium, the cords are destined to become seminiferous tubes and in the ovary they remain as abortive seminiferous tubes, known as medullary cords. Thus, under the term medullary cords are understood the epithelial formations of the fetal ovary deriving from the first proliferation of the germinal epithelium and homologous to the seminiferous tubes in the male. If the gonad is destined to become a male gonad, the cords perfect themselves, lose their lateral anastomoses and organize into true seminiferous tubes. The germinal epithelium covering the surface of the gland disappears, the connective tissue undergoes condensation and forms testicular albuginea and between the tubules there appear large acidophilic interstitial cells. In the gonad that is destined to become an ovary, the germinal epithelium, after having produced the medullary cords, does not lose its aptitude to multiply and forms the second set of sexual cords—the cords of Valentin-Pflüger—which arise as a secondary proliferation of the germinal epithelium. According to Winthwaite and Sannmont, Valentin-Pflüger's cords of the ovary transform themselves into primordial follicles without giving rise to primitive ovules. Some of them reach only the stage of primordial follicles, others are transformed into graafian follicles, more or less voluminous but with the same doom awaiting them. After degeneration of the derivatives of the second proliferation—degeneration which occurs after birth—the germinal epithelium undergoes a new period of multiplication by invagination and it is from the cellular colonies of this third proliferation that a definite cortical zone and definite ovary are formed. While the genital portion of the mesonephron in the male gonad takes an actual part in the building of the genital organs and forms the proximal part of the efferent ducts, in the female it remains nonfunctioning and absolutely rudimentary as the rete ovarii and efferent canaliculi of the epoophoron. The tubular embryonic duality persists rudimentarily but constantly and as an unutilized tubular constituent remains in the ovary in the form of embryonic vestiges giving rise to the anomalies described.

If the degeneration of the medullary cords led to their complete and indisputable disappearance, the anomalies arising from the medullary cords should not take place at all. However, it is admitted now that certain genital anomalies, for instance spontaneous sex reversal or the experimental transformation of the ovary into testis or ovotestis, have to be interpreted either as the result of the presence within the ovary of the remains of medullary cords or as a manifestation of the retained potency of the germinal peritoneal epithelium to proliferate.

and, by duplicating the embryonic process, to form anew the sex cords in such ovaries. This possible dual source of morphologic disturbances of the ovaries must be considered always in the studies of certain embryonic ovarian tumors. The development of such tumors is in many instances preceded by profound changes of the gonads with hyperplasia of the embryonic epithelial vestiges and their gradual organoid arrangement and transformation into intersexual glands or ovotestes. During these changes the female structures of the ovarian cortex undergo regression, and with their disappearance the ovary loses control over the embryonic vestiges, which then begin to grow, differentiate in the male direction and later by their hormonal action influence the secondary sex character. Thus clinical manifestations with disturbance or suppression of menstruation and the psychic and somatic stigmas of masculinization find explanation and should be expected in cases of embryonal tumors of germinal origin. This suggests that such tumors are etiologically related to gonadic misbuilding and disturbances and often are the sequence of the latter.

The earlier investigators of tubular adenomas of the ovary (Pick¹ Schickele²⁶) were inclined to associate these tumors always with hermaphroditism or pseudohermaphroditism. Neumann³ and Meyer² insisted justly that, although such tumors are more common in persons with rudimentary genitalia, they may occur as well in perfectly normal women. Of course Pick's definition of hermaphroditism differs from that generally employed. According to Pick, essential hermaphroditism lies in the mixing of germinal sexual characters or the union of male and female characters independently of order, degree of development or actual stage of morphologic sexual differentiation. The zoologic definition of hermaphroditism implies the union in the same person of the primary sexual characters of both sexes or the simultaneous existence of female and male gonads (Caridroit²⁷). Meyer's opinion, as I shall show later, has more reason to be accepted than that of Pick since it is backed by the substantial support of zoologists with their more exact methods of observation and experimentation.

Neumann trying to reconcile the opposite opinions of Meyer and Pick, asked why one should not use instead of the term hermaphroditism the term "potential hermaphroditism." This term, of course, may be proper in a physiologic sense, but morphologically it sounds one-sided and meaningless as compared with the zoologic term sex reversal or

26 Schickele, G. Adenoma Tubulare Ovarii (Testiculare), Beitr. z. Geburtsh. u. Gynak. **11** 263, 1907.

27 Caridroit, F. Étude histo-physiologique de la transplantation testiculaire et ovarienne chez les gallinacées, Bull. biol. de la France et de la Belgique **59-60** 135, 1925-1926.

intersexuality The latter term designates the state of the gonad which changes its sex spontaneously or experimentally, prenatally or post-natally, and undergoes structural evolution with transformation of the ovary into ovotestis or rudimentary testis Strictly speaking, there is no true hermaphroditism in man since true hermaphroditism means the union of the organs of two sexes which are capable of functioning, and the last or simultaneous and successive formation of two sorts of gametes in the same organ has never been observed (Lacassagne²⁸) The term hermaphroditism, said Professor Lillie,²⁹ has so many connotations that it seems better to drop it from one's vocabulary so far as mammals are concerned and designate these questionable sexual anomalies under the head of intersexual His own work and the work of his associates on free-martins should be consulted by medical students of this problem, since it gives essential information, closely related to the pathology of the human ovary and its embryonal neoplasms of the tubular testicular type

In order to understand the part which medullary cords may play, both in sexual metamorphosis of the female gonad and in etiology of the tubular testicular adenomas, one must first briefly review the latest work on gonadic transformation in free-martins, after x-ray irradiation, in ovarian grafts and after a left-side oophorectomy in birds This review will contribute, in addition, a great deal to a proper interpretation of the nature of the large clear, fat-laden cells present also in the tumor described by me and wrongly interpreted by some writers on ovarian testicular adenomas as interstitial Zwischenzellen

Under the term free-martin, I understand a female which is born a co-twin with a normal male of cattle, goats or pigs and which has the internal reproductive organs of the male type and the external genitalia of the female type At first it was considered as an abnormal male, but later the conclusion was reached that primarily the free-martin gonad is female in structure and that secondarily it is transformed into a male gonad In accordance with the degree of transformation, the gonads of the free-martin are divided into three groups characterized respectively as the low, the medium and the high degree of transformation in the male direction (Willier³⁰) Gonads of the "low degree" of transformation are characterized by an undescended or ovarian position, by the absence of epididymis, by the

28 Lacassagne, A La question de l'hermaphroditisme chez l'homme et les mammiferes, *Gynec et obst* **1** 273, 1920

29 Lillie, F R The Free-Martin A Study of the Action of Sex Hormones in the Foetal Life of Cattle, *J Exper Zool* **23** 371, 1917

30 Willier, B H Structures and Homologies of Free-Martin Gonads, *J Exper Zool* **33** 63, 1921

small size and low degree of the organization of the sex cords and by a large and well differentiated rete, penetrating to the posterior end of the medullary cords but still retaining its primitive position at the hilum of the ovary. Gonads of the "medium degree" of transformation show a further step toward testicular organization. The gonads still retain the ovarian position, but the sex cords appear larger and show a high degree of organization with the establishment of a connection with the rete cords. Two types of sexual cords are recognizable. One type resembles the medullary cords and the other seminiferous tubules. The former corresponds in its appearance to the medullary cords of the normal ovary, being composed of solid strands and cords or irregularly arranged and closely packed epithelial cells forming a syncytium which may be regarded as the primordium of a Sertoli cell syncytium. The transition between medullary cords and seminiferous tubules can be definitely observed at this stage. The gonads of the "high degree" of transformation are descended to a position in the groin, the seminiferous tubules are well differentiated, the tubuli recti connect the rete tubules with the seminiferous tubules, the rete tubules connect with the vasa efferentia, the epididymis is typically male and a typical spermatic cord is present.

The described phenomenon of the gradual transformation of the gonad demonstrates that a gonad with a primary female determination may form a structure which is morphologically a testis. This is accomplished through suppression of the cortex and overdevelopment of the medullary cords and urogenital union. The observation on free-martins proves that the gonad of mammalian female zygotes is capable of a series of transformations that may exist between an ovary and a testis. I shall discuss later the nature of the etiologic factors causing such transformation. Having presented the conceptions of Lillie,³⁰ Willier,³⁰ Hughes³¹ and Chapin,³² I shall proceed with a discussion of post-irradiation transformation of the ovaries.

In a series of publications Brambell, Parkes and Fielding³³ presented important observations on the morphologic changes that take place in the ovary of the mouse following exposure to x-rays before

31 Hughes, W. The Free-Martin Condition in Swine. *Anat Rec* **41** 213, 1929.

32 Chapin, C. L. A Microscopic Study of the Reproductive System of Foetal Free-Martins, *J Exper Zool* **23** 453, 1917.

33 Brambell, F., Parkes, A., and Fielding, U. Changes in the Ovary of the Mouse Following Exposure to X-Ray Irradiation at Three Weeks Old. *Proc Roy Soc London (ser B)* **101** 29, 1927, Changes in the Ovary of the Mouse Following Exposure to X-Ray Irradiation at or Before Birth, *ibid* **101** 95, 1927. Brambell, F., and Parkes, A. Changes in the Ovary of the Mouse Following Exposure to X-Ray Irradiation of the Nonparous Adult, *ibid* **101** 316 1927.

birth, at birth and at the age of 3 weeks. In the case of irradiation of the ovary of the mouse at 3 weeks of age, following destruction of the follicles, the ovary shows, at about the twenty-fourth postirradiation day, a remarkable phenomenon manifested by proliferation of the germinal epithelium and its growth into the cortex in the form of thick, finger-shaped cords carrying with them a layer of cells of the tunica albuginea. When the cords reach the hilar region of the medulla, their growth ceases, the germinal epithelium stops proliferating and becomes thin and inactive and the cells composing the cords undergo hypertrophy, accumulate fat globules and transform into large, clear cells strikingly resembling luteal tissue. The fact that at this stage these fat-laden, clear cells are still in the form of finger-shaped cords with only thin connective tissue sheaths serves to distinguish them from corpora lutea vera or from corpora lutea atretica. The ovaries of some animals appear to remain in this stage and never go beyond it, however long they are observed. The ovaries of other animals, having arrived at this stage, undergo still further changes. The germinal epithelium reveals a second proliferation, distinct from the first, with the production of small masses or cords of cells which become separated from the surface epithelium almost as soon as they are formed. The tunica albuginea contributes connective tissue sheaths to these cords of the second proliferation and the nuclei of some of the cord cells become slightly enlarged, exhibit mitoses and undergo evolutionary changes suggestive of spermatogonia in embryonic testicular tubules. As Brambell stated, the epithelial cords of the second postirradiation proliferation of the germinal epithelium tempt comparison with those which during embryonic and prepubertal life normally take part in the organogenesis of the mammalian gonads. The origin of the cords of both the first and the second postirradiation is similar to that of the medullary and cortical cords of the normal ovary and of the spermatogenic tubules of the testis. The resemblance of these cords of the second proliferation to the structures described as spermatogenic tubules is remarkable. Thus, after exposure to the x-rays, the female gonad of the young mouse shows all the morphologic signs of sex reversal, with the formation of cords which are similar in every way to the sex cords of the free-martin.

When ovarian grafts are made in embryonic chicks (Greenwood³⁴), and in young chicks (Greenwood,³⁵ Finlay³⁶) and when ovarian auto-

34 Greenwood, A. W. Gonad Grafts in Embryonic Chicks and Their Relation to Sexual Differentiation, *Brit J Exper Biol* **2** 165, 1924-1925.

35 Greenwood, A. W. Gonad Grafts in the Fowls, *Brit J Exper Biol* **2** 469, 1924-1925.

36 Finlay, G. F. Studies on Sex Differentiation in Fowls, *Brit J Exper Biol* **2** 439, 1924-1925.

plastic transplants are made to hens (Candroit,³⁷ Benoit³⁸), the grafts may show remarkable changes in the direction of sex reversal. Here these changes may show all grades of morphologic evolution beginning first with the formation of irregular epithelial structures resembling syncytium, then development of the cords and finally differentiation into tubes resembling absolutely the seminiferous tubes of normal testicles. The epithelial elements which have not shown evolutionary differentiation become loaded with fat and are destined to give rise to clear cells like interstitial cells which differ from the mesenchymal Leydig's cells and for this reason are called by Candroit simply "cellules claires". The source of the described syncytial formations, cords and tubes in ovarian grafts according to Candroit³⁷ may be triple: (1) the germinal epithelium, (2) nonutilized medullary cords of the first proliferation lodged in the theca and not transformed into clear cells, and (3) stroma cords arising from the secondary embryonic proliferation. The rapid neoformation of a testicular nature that takes place in the autoplasmic ovarian transplants repeats completely the embryonal process, and the graft undergoing such transformation into a testis should be called an intersexual gland.

In both spontaneous sex reversal in the hen (Fell³⁹) and in testicular transformation of the right gonad after left side oophorectomy in the hen (Benoit³⁸) the process of transformation follows the same sequence of changes as were described for ovarian grafts. It is important to mention here that the fragments of the left ovary which have escaped during oophorectomy may regenerate and transform themselves into an organ composed of cords and tubes of male aspect (Benoit³⁸).

All investigators on sex reversal come to the following conclusions: (1) that the testes are remarkably stable while the ovaries possess a certain instability, (2) that the right ovary exhibits testicular transformation more often than the left one and (3) that in sex reversal or hermaphroditism in which an ovotestis is present the spermiatic tissue occurs most commonly median to the ovarian position. The embryologic development of the gonads furnishes an explanation for the first conclusion regarding the stability of the testis. As Lilhe⁴⁰ stated: "Theoretically we would have to assume that the male zygote contains female as well as male factors, but the male zygote may not be capable of such extensive transformation as the female owing to the embryologic fact

37 Benoit, J. Origine des cordons sexuels d'aspect male apparus dans des régénérat et des greffons ovariens chez la poule, *Compt rend Soc de biol* **94** 875 1926

38 Fell, H. B. Histological Studies of the Gonads of the Fowl *Brit J Exper Biol* **1** 97, 1923-1924

39 Benoit, J. États sexuels différents successifs obtenus expérimentalement chez une même poule *Compt rend Soc de biol* **94** 1380, 1926

that the male gonad never forms normally any homologue of the cords of Pflüger in the female, i e., of the ovarian cortex, whereas the female does form the homologue of seminiferous tubules before the cords of Pflüger begin to arise." An additional reason for the stability of the male gonad is that since the early sex differentiation of the female presumably takes place solely under zygotic control while differentiation of the male is controlled by sex hormones, the introduction of female substance into the male system is without effect on the growth of the testes. The primary action of the sex hormones is the inhibition of growth of germinal epithelium. Thus, the introduction of male substance into the female system may overcome zygotic influence and suppress the growth of the cortex (Hughes³¹)

The preponderance of gonadic disturbances on the right side in the female is not limited to the lower vertebrates or birds only. If one reexamines the reports of cases of sex reversal or hermaphroditism in higher animals and in the human species, one finds also the predominance of right-side disturbances. This is not a simple coincidence, but evidently is the result either of quantitative inequality of the gonads or certain mechanical and vascular factors that make the ovary of the left side more stable as compared with the right one. Of nine pigs of intergrade sex, described by Baker,⁴⁰ seven showed testes on both sides and two, testes only on the right side, a normal ovary being present on the left side. In Corner's⁴¹ hermaphroditic adult pig, a testis with epididymis was found on the right side in place of an ovary. Nine reports of cases of hermaphroditism collected by Pick⁴² show the same predominance of a right-side disturbance. Three of these reports do not have any data concerning a left-side gonad, and yet in spite of this and the absence of germ cells in the testicular portion Pick classifies the cases as cases of hermaphroditismus verus. A striking predominance of male or mixed gonads on the right side in human hermaphroditism is evident from publications by various authors. Of eight reports of cases of human hermaphroditism collected by Lacassagne,²⁸ four dealt with mixed glands or ovotestes found only on the right side, two with ovotestes found on both sides, one with a testis found on the left side and an ovotestis on the right side and one with a true testis found on the right side and an ovary found on the left side. Baldwin's⁴³ patient

40 Baker, J. R. On Sex Intergrade Pigs Their Anatomy, Genetics and Developmental Physiology, *Brit J Exper Biol* **2** 247, 1924-1925

41 Corner, G. W. A Case of True Lateral Hermaphroditism in a Pig with Functional Ovary, *Contrib Embryol* **54** 137, 1920

42 Pick, L. Ueber den wahren Hermaphroditismus des Menschen und der Säugetiere, *Arch f mikr Anat* **84** 119, 1914

43 Baldwin, J. F. Lateral Partial Glandular Hermaphroditismus, *Am J Obst & Gynec* **2** 640, 1921

had, on the right side, testicular tissue and on the left side, an ovary. Of eight reports of cases of gonadic tumor with probably a male gonad on the other side collected by Neumann,⁴⁴ all describe right gonads showing male elements. According to Simpson (quoted by Willier⁴⁵), in the human female the left-side gonad is of pure female type, and disturbances, if present, are usually found in that on the right side. Zoologic observations show that disturbances in relation of parts in the fetal stage are found most commonly on the right side and that differentiation of ovarian tissue does not proceed so far in the right ovary as in the left. Thus the right ovary, as less differentiated tissue, is more capable of completing its differentiation or redifferentiation in a testicular direction than is the more highly differentiated tissue of the left ovary. About 65 per cent of young calves show the left ovary to be larger than the right, and the follicles more advanced. In birds, the right ovary is a rudimentary ovary (Riddle⁴) or, according to Benoit,⁴⁶ it is a rudimentary testicle and after a left oophorectomy this rudimentary right gonad shows definite redifferentiation in a testicular direction. Firket's⁴⁶ and Swift's⁴⁷ studies on the primordial germ cells of the chick explain this phenomenon on the basis of an initial primitive quantitative inequality of the two gonads as the result of an uneven distribution of the germ cells such that a greater number of germ cells lodged in the left genital ridge than in the right. These interesting embryologic observations may serve as a supplement to both the theory of a better supply of blood to the left ovary and the theory of a sex hormone.

The experimental material and observations that have been presented contribute greatly to the proper understanding of prenatal and postnatal gonadic misbuilding and, in addition, this knowledge of the sex reversal of the ovaries removes the necessity of associating testicular adenomas of the ovary always with hermaphroditism. Histologic study of the ovotestis indicates that the mixed gland originally was a normal ovary which progressively changed into a testis. Male transformation of the ovary has its cause in the glandular tissue itself. This means that in case of gonadic transformation no new structures are formed and the testicular tissue found does not constitute a sort of extrinsic tumor, for a primordium of each male structure developed is present in the ovary at the time of sex differentiation. Gonadic redifferentiation of the

44 Neumann (footnote 3 third reference)

45 Riddle, O. On the Sexuality of the Right Ovary of Birds, *Anat Rec* **30** 365, 1925

46 Firket, J. Recherches sur l'organogenèse des glandes sexuelles chez les oiseaux, *Arch de biol* **29** 201, 1914

47 Swift, C. H. Origin of the Definitive Sex Cells in the Female Chick, *Am J Anat* **18** 441 1915

ovary in the male direction is observed in various conditions, and sex reversal can be influenced or initiated by various factors. For instance, spayed females of certain birds and animals tend to develop male characters, heifers with cystic degeneration of the ovary reveal the same tendencies, excessive egg-laying in birds may stimulate a new proliferation of sex cords, abdominal pathology, abdominal tuberculosis, surgical trauma, hemorrhages and ovarian neoplasms can also initiate redifferentiation of the ovary in the male direction. It appears that diminution of the ovarian mass or anything causing suppression of the ovarian cortex or leading to the degeneration of the follicles and diminution of the number of oocytes can upset the balance held by the oocytes, and possibly by the membrana granulosa, as female tissues acting against masculinizing substances, and initiate either organoid or neoplastic growth of male epithelial formations arising from the cords of the first and the second proliferation (Crew,⁴⁸ Caudoit²⁷ Masson,¹¹ Masson Chaher and Martin⁴⁹). It is interesting to mention here that neoplasms of the seminiferous type arising from medullary cords of the first proliferation are not found in mares, and this may be explained on the embryologic basis that no first proliferation initially male is observed in the development of the mare's ovary (Corsy⁵⁰). The quoted work of Brambell, Parkes and Fielding shows that the initial stage of sex reversal can be produced experimentally in the mouse by the action of the x-rays on the ovary and that in this case the germinal epithelium itself can give rise to a new proliferation in the form of sex cords. Keller's⁵¹ studies on normal and pathologic activity of the germinal epithelium in various types of adult ovaries collected by Champy favor such a possibility, especially in pathologic conditions. Keller mentioned also that small invaginations of the germinal epithelium may form nodules resembling in every way interstitial tissue. In cases of sex reversal in pigeons, the sex cords, according to Brambell,⁵² are derived from large clear islet cells genetically related to medullary cords and scattered in the ovarian stroma and in the theca, and morphologically resembling in every respect the luteal or interstitial cells of other authors.

48 Crew, F. A. Studies in Intersexuality, Proc Roy Soc London (ser B) **95** 90, 1923, **95** 226, 1924

49 Masson, P., Chaher, A., and Martin, J. Varicocèle tubo-ovarien. Oo-testis avec adenomatose testiculaire diffuse, Ann d'anat path **2** 445, 1925

50 Corsy, F. Les neoplasies du testicule du cheval et leur importance pour l'embryologie et la pathologie generales de l'epithelioma semmiere. Bull de l'Assoc franç p l'etude du cancer **16** 218, 1927

51 Keller, T. L'activite normale et pathologique de l'epithelium germinatif de l'ovaire adulte, Gynec et obst **17** 10, 1928

52 Brambell, F. Sex Reversal in a Pigeon, Proc Roy Soc London (ser B) **104** 459, 1929

In my case the growth reached a considerable degree of differentiation with morphologic formations of embryonic male type. The hormonal influence was sufficient to cause the genital changes with suppression of the cortical activity of both ovaries and consequent cessation of menstruation. No signs of secondary sex changes were present, and nothing would justify the association of the tumor in my case with hermaphroditism in the biologic sense. This proves once more the correctness of Meyer's⁵³ opinion regarding the occurrence of testicular tubular adenomas in nonhermaphroditic persons. Shortly after removal of the tumor, normal menstruation was reestablished and in May, 1928 the patient was readmitted to this hospital and gave birth to a perfectly normal female child.

The discussion presented amplifies to a great extent the difficult question of the origin of tubular testicular adenomas of the ovary and also increases one's knowledge of various possibilities and causes of ovarian sex reversal. The presence of cells like lutein or interstitial cells in this tumor necessitates more careful morphologic differentiation between true *Zwischencellen*, or Leydig's interstitial cells of connective tissue origin, and the large clear, fat-laden cells present in my tumor and found also in embryonic ovaries and testicles and originating from epithelial elements of medullary or sex cords (Brambell,⁵⁴ Nonidez,⁵⁵ Simkins,⁵⁶ Popoff,⁵⁷ Caridroit,⁵⁸ Benoit,⁵⁹ Athias⁵⁹ and Aron⁶⁰). The fact that in most of these tumors the spermatogenic tissue occurs median to the ovarian position may be explained by the favorable conditions existing in the hilum, where loose connective tissue and good vascularization offer better facilities for the growth of sex cords than do the dense structures of the cortex (Fell⁵⁴).

53 Prof. Dr. Robert Meyer of Berlin, examined the slides submitted and gave his help in the matter of diagnosis.

54 Brambell (footnotes 33 and 52).

55 Nonidez, J. F. Studies on the Gonads of the Fowl. The Intertubular Tissue of the Testis in Normal and Henfeathered Cocks, *Am J Anat* **34** 359, 1924, Studies on the Gonads of the Fowl. The Effect of Ligation of the Vas Deferens on the Structure of Testis *ibid* **34** 393, 1924.

56 Simkins, C. S. Origin of the Sex Cells in Man, *Am J Anat* **41** 249, 1928.

57 Popoff, N. Le tissu interstitiel et les corps jaunes de l'ovaire, *Arch de biol* **26** 483, 1911.

58 Benoit, J. Sur l'origine des cellules interstitielles de l'ovaire de la poule. *Compt rend Soc de biol* **94** 873, 1926.

59 Athias, M. Recherches sur les cellules interstitielles de l'ovaire des cheiropteres, *Arch de biol* **30** 89, 1920.

60 Aron, M. Sur la glande interstitielle du testicule embryonnaire chez les mammiferes, *Compt rend Soc de biol* **85** 107, 1921.

CONCLUSIONS

A case is described of tubular testicular adenoma of the ovary which occurred in a woman free from any signs of hermaphroditism.

Biologic observations and experimental data on sex reversal and gonadic disturbances of the ovary are presented and commented on, and the conclusion is drawn that morphologic peculiarities of the ovary and biologic factors determining sex differentiation offer a logical explanation of spontaneous reactivation of the medullary cords, and even of the germinal epithelium, with the consequent organoid transformation in a male and neoplastic direction.

In studies of clinical material and in histologic research in the ovary, attention should always be given to a full recording of the observations in both gonads and to a quantitative study of the occurrence of gonadic disturbances on the right side.

The large, clear, fat-laden cells found in tubular testicular adenomas and originating from epithelial elements of medullary or sex cords should not be confused with true interstitial cells of connective tissue origin.

Embryologic considerations, zoologic observations and experimental data give every preference to the term sex reversal or intersexuality rather than the meaningless term hermaphroditism which is generally used now.

DETORSION DEFECTS IN CONGENITAL CARDIAC ANOMALIES

REPORT OF THREE CASES WITH AN ANALYSIS OF THE MECHANISM OF THEIR FORMATION *

PHILLIP F. SHAPIRO M.D.

CHICAGO

Although congenital deformities of the heart are rather infrequent in the course of time there has appeared in the literature an impressive number of reports of cases. The anomalies appear in infinite variety. They form endless combinations of various cardiac abnormalities with one another and with associated defects in other organs. Despite the complexities which they sometimes offer they subscribe to definite anatomic laws and by them may be analyzed. This and the fact that each case lends an insight into normal cardiac embryology and into its vagaries have combined to give these deformities an interest that even exceeds their clinical importance.

Three such cases have come to my attention. They combine so many unusual cardiac anomalies that their analysis embraces a large part of the field of cardiac embryology. By chance they formed a series of defects a new explanation for the mechanism of which was recently propounded by Spitzer¹ and discussed by Monckeberg.²

REPORT OF CASES

CASE 1—A colored boy, aged 14 months, was the youngest of five children. Parents and siblings were apparently normal. The child's birth and feeding were normal, but he had never been able to put on weight. In the last three months he began to lose rapidly what weight he had attained. A persistent cough developed and a daily afternoon fever was noted. In the last four weeks a diarrhea of from four to five stools a day alternated with constipation.

The temperature was 103.6 F., the pulse rate 130. Moist rales were heard in both lungs. The cardiac apex impulse was in the right nipple line but there were no murmurs, no cyanosis and no dyspnea. The abdomen was distended and tympanitic. The hemoglobin per cent was 80, the red blood cell count was 4,630,000.

* Submitted for publication, Aug. 27, 1929.

¹ From the Department of Pathology of the Cook County Hospital.

1. Spitzer, Alexander. Ueber den Bauplan des normalen und missbildeten Herzens, Virchows Arch. f. path. Anat. **243**: 83, 1923.

2. Monckeberg, J. G. Die Missbildungen des Herzens, in Henke and Lubarsch, Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

and the leukocyte count was 10,700, with 80 per cent polymorphonuclear cells. The result of the Pirquet test was negative. But the x-ray picture confirmed the clinical diagnosis of tuberculous bronchopneumonia and congenital dextrocardia.

At autopsy, the child was found to be severely emaciated. Though he had grown to a normal height of 68 cm, both anterior and posterior fontanelles were still open and the teeth had not erupted. After the development of a fibrocaseous tuberculous primary lesion in the left upper pulmonary lobe and the caseation of the hilar lymph nodes draining the region, tuberculous cavities in the right lung had developed and an ulcerous ileitis. An acinose-nodose and miliary tuberculosis of both lungs terminated the case.



Fig 1 (case 1) —Deformity of the heart viewed from the right. The letters indicate *a*, rete Chiari, *b*, common auricular cavity, *c*, common atrioventricular, *d*, vestige of the auricular septum, *e*, left ventricle, *f*, ventricular septal defect, tricuspid valve leaflet and *h*, right ventricle.

No trace of the spleen nor of a splenic artery was found. The abdominal lymph nodes were enlarged to a diameter of 11 mm, and were discrete and reddish gray. Histologic examination of the nodes revealed numerous caseated tubercles with huge giant cells containing as many as a hundred nuclei. The liver showed a much larger left lobe than normal.

Heart—The heart weighed 50 Gm. It lay with its apex in the right mid-clavicular line. It presented a large, common auricle leading through a common auriculoventricular opening into an incompletely divided ventricular chamber, which emptied through a single arterial trunk.

The large common auricle had a small right and a larger left auricular appendage. Its interior was crossed sagittally by a sparse network of fine fibers. This net began at the right margin of the coronary sinus and inserted itself at the crista terminalis on the dorsocranial wall of the auricle. The pulmonic veins, which had united opened by a single trunk just to the left of this insertion of the net, and the venae cavae to its right. No further semblance of an interauricular septum could be found except a heavy muscular trabecula from 1 to 2 mm thick. It stretched almost in the same plane as the net, across and just above the common auriculoventricular orifice.

This opening 18 mm in diameter led into a large ventricular cavity. The cavity was divided incompletely and with marked inequality by a rudimentary



Fig 2 (case 1) —Deformity of the heart, viewed from the left. One may note the three semilunar cusps and the two coronary orifices. The letters indicate *a*, single arterial trunk; *b*, hypertrophied left ventricle; and *c*, bicuspid leaflet.

septum into a large left ventricle and a small right one. The septum reached 12 mm, barely half its required height. Its concave upper edge thus left a gaping orifice 9 mm in diameter between the ventricles. The insignificant right ventricle had a cavity from but 1 to 2 mm wide, and was buried altogether beneath a large valve leaflet of the common auriculoventricular orifice.

Three leaflets guarded this opening. One originated from the entire right half of the auriculoventricular ring. It straddled the incomplete ventricular septum, covering the defect. It attached itself by three groups of chordae tendineae into the left ventricle side of the septum and thus shut out the entire right ventricle.

No leaflets, at all, inserted themselves into the right ventricular cavity itself. A second, large one hung into the left ventricular cavity, and was attached by two groups of chordae into the posterior and left lateral walls. This leaflet was 14 mm wide, and apparently was the most effective one in auriculoventricular closure. The ring was completed by a third small leaflet with a single group of chordae attached to the anterior wall of the left ventricle.

The enlarged left ventricle formed the apex of the heart. It formed practically the entire ventricular chamber. Internally it was 22 mm in transverse, 18 mm in anteroposterior and 22 mm in longitudinal diameter. Its wall was 9 mm thick. This large chamber opened by a single arterial trunk. From the left wall of the vessel, a small ridge extended into the anterocranial corner of the ventricular cavity. It reached in the line of the sulcus longitudinalis anterior toward the interventricular septum, and reduced somewhat the size of the defect of the latter. The large bicuspid auriculoventricular leaflet originated just to the left of this ridge.

No trace of a second arterial trunk was found. The single large vessel rested in the groove between the auricular appendages. It had three semilunar cusps, a left and a right each with a coronary orifice, and an anterior without. The coronary artery originating from the right sinus of Valsalva divided into a descending branch to the sulcus longitudinalis anterior, and a circumflex branch around the left side of the heart. Thus it really corresponded in distribution to the left coronary artery. That originating in the left sinus of Valsalva descended into the sulcus longitudinalis posterior. Thus it corresponded to the right coronary artery.

Two centimeters above the cusps, two vessels were given off. One directly supplied the left lung. The other promptly divided into an innominate artery and a vessel which led to the right lung. The left common carotid and subclavian arteries arose at a slightly higher level.

Summary—The congenital defects in this case include

- (1) Dextroversio cordis
- (2) Widely patent foramen secundum and primum atriorum, with absence of the septum secundum and spurium
- (3) Rete Chiari atriorum
- (4) Single pulmonary vein
- (5) Common auriculoventricular orifice with fusion of the tricuspid valve leaflets
- (6) Defective interventricular septum
- (7) Rudimentary right ventricle and hypertrophied left ventricle
- (8) Solitary truncus arteriosus aorticus with complete absence of the pulmonary artery
- (9) Detorsion defect of the truncus aorticus with reversal of the coronary arteries
- (10) Origin of the pulmonary arteries (left) from the aorta and (right) from the innominate artery
- (11) Aplasia of the spleen

CASE 2—A white female infant had lived only to the age of 2 months. She was the youngest of nine children. The others were normal. This the last child, for no apparent reason had failed to gain weight properly. She was dull and apathetic, and suffered from attacks of marked restlessness accompanied by a slight cyanosis and an occasional nosebleed.

Physical examination revealed poor nutrition a bilateral coloboma of the iris and a mongoloid face. A slight cyanosis was noted, but no cardiac disturbances. The abdomen was distended. The liver, spleen and both kidneys were palpable. The hemoglobin per cent was 100, the erythrocyte count was 4,180,000 and the white blood cell count was 10,200, with 74 per cent polymorphonuclear cells. A trace of sugar and of albumin and many granular casts were found in the urine. The temperature rose terminally to 103.6 F, and a deep cyanosis developed.

Heart—At autopsy (by Dr. R. H. Jaffe) the heart was in its normal position. It was somewhat larger than usual, but made up equally of both ventricles. It weighed 38 Gm., and was 50 mm. in transverse, and 45 mm. in longitudinal and in anteroposterior diameters.

When the heart was opened, two abnormal communications were found between the two chambers. One in the interauricular septum was oval, not valvelike, and

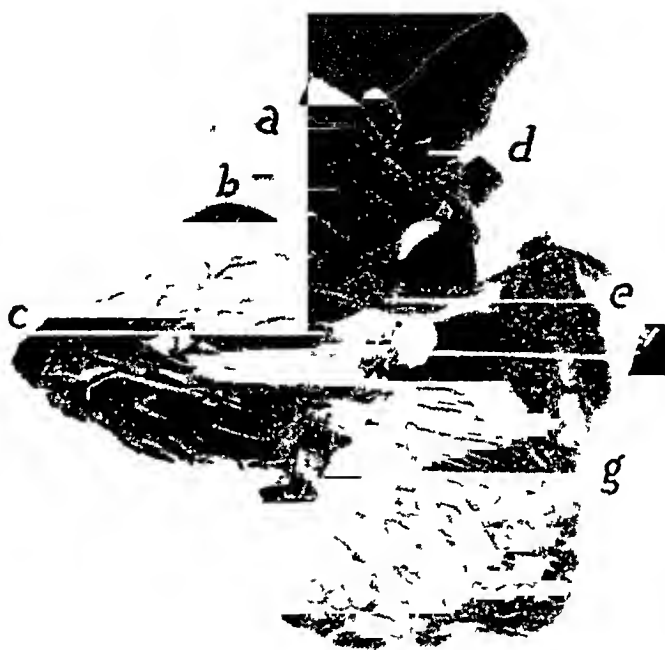


Fig. 3 (case 2)—The right ventricle. The letters indicate *a*, aortic arch, *b*, right pulmonary artery, *c*, aortic valve, *d*, ductus Botalli, *e*, pulmonary valve, *f*, defect in septum and *g*, tricuspid valve.

about 3 by 5 mm. in diameter. It was located at the base of the septum 3 mm. from the mitral and tricuspid rings. Except for this intercommunication, the two atria were normal. The atrioventricular openings were also normal, the right 40 mm. in circumference, with three leaflets, the left 30 mm., with two.

The other defect was in the base of the interventricular septum, and was 7 by 8 mm. The two ventricles were of about the same size. The wall of the left ventricle was from 5 to 6 mm. thick, that of the right from 6 to 7 mm. thick. The left ventricle had no outlet except through the defect in the ventricular septum. Its vessel, the aorta, was found to originate entirely from the right ventricle.

Both the aorta and the pulmonary artery arose from the right conus. The aorta occupied a position posterior to but abnormally to the right of the pulmonary

artery The aortic orifice was below the pulmonary valves, and separated from the septal defect by a fibrous fold 2 mm thick It was 5 by 7 mm in diameter, and closed by two irregular cusps that did not appear to be adequate The pulmonary orifice was larger, 9 by 10 mm in diameter, and closed by three well developed cusps

The aorta and the pulmonary artery were connected by a patent ductus arteriosus 5 mm long, with an internal diameter of 4 mm It opened into the aorta 23 mm from its orifice and 5 mm from the origin of the left subclavian artery It started from the pulmonary arch, 10 mm distal to its orifice, just anterior to the origin of the left pulmonary artery

Only one coronary artery was present It originated in the sulcus between the anterior aspect of the aorta and the pulmonary artery It divided at once into two equal branches One passed down the sulcus longitudinalis anterior to the



Fig 4 (case 2)—The left ventricle The letters indicate *a*, aortic arch, *b*, left auricle and *c*, common coronary artery

apex, the other passed to the right and posterior aspects of the heart Thus it corresponded to the distribution of both coronary arteries

Kidneys—The other significant abnormalities were in the kidneys These were larger than normal, the right weighing 24 Gm and the left, 30 Gm On both the external and the sectional surfaces of the cortex, many small, round, gray patches were just visible to the naked eye An aberrant suprarenal gland, 3 mm in diameter, rested in the hilum of the left kidney

Histologic examination of the kidneys showed the numerous round gray patches to represent cysts It offered a complete picture of the development of these cysts by gradual distention of the Bowman's spaces of the glomeruli, with compression atrophy of the capillary tufts The cysts of the medulla seemed to have developed from the ducts

No permission was granted for an examination of the head

Summary—The congenital defects in this case number

- (1) Patent foramen ovale
 - (2) Defect in the interventricular septum
 - (3) Dextroposition of the aorta with complete origin of both arterial trunks from the right ventricle (detorsion defect)
 - (4) Common coronary artery
 - (5) Patent ductus arteriosus
 - (6) Hypertrophy of the right ventricle
- Defects associated with the cardiac ones were
- (7) Mongoloid idioey
 - (8) Bilateral coloboma of the iris
 - (9) Polycystic kidneys

CASE 3—A colored male infant 5 weeks of age, was the second child of a healthy family, and had had a normal birth. Respiratory difficulty, relieved by rest, had been noted since birth. This was suddenly aggravated six hours before admission to the hospital. There were no convulsions, no cyanosis and no abnormal cardiac sounds.

No respiratory obstruction was found. The thymic area was wide to percussion. The pharynx was injected, and a few rales were heard posteriorly. The temperature was 97.6 F. Two days later, the child came to autopsy with a clinical diagnosis of thymic dyspnea or early bronchopneumonia.

The thymus was found to be of practically normal size, 8.5 Gm. No pneumonia, but a focal atelectasis of both lungs, was present.

Heart—The essential abnormalities were in the heart. It weighed 41 Gm and was markedly enlarged. It was 55 mm in transverse, 45 mm in anteroposterior and 50 mm in longitudinal greatest diameters. It lay with its apex in normal right position, but was strikingly asymmetric. Externally, it could be seen that the sulcus longitudinalis, displaced to the right, separated a small right ventricle from a much larger left ventricle. The apex was formed entirely by the enlarged left ventricle.

The left ventricle was 20 mm wide, 22 mm deep and 30 mm long in its internal diameters. Its wall was 7 mm thick. The right ventricle measured only 14 by 16 by 24 mm, in the corresponding diameters. Its wall was only 2 to 3 mm thick. The right and the left ventricles were separated by an interventricular septum 21 mm high, which was incomplete in its upper portion, leaving an interventricular septal defect, 15 by 12 mm in diameter.

Riding squarely over the septum and its defect was an enlarged pulmonary trunk. It had a circumference of 30 mm and was closed by three semilunar cusps, a left, an anterior and a posterior. The left and right pulmonary branches were given off 7 mm above the left and posterior cusps, respectively. The trunk then terminated in a widely patent ductus arteriosus. The ductus was 7 mm long. It was funnel-shaped, so that its pulmonic end was 3.5 mm in diameter and its aortic end only 2 mm in diameter.

The aorta maintained an abnormal position anterior to and to the right of the pulmonic trunk. It issued from the right anterior corner of the right ventricle by a narrow orifice. Rather smaller than the pulmonic trunk, it had a circumference of only 18 mm. At the isthmus there was an abrupt narrowing to a circumference of 10 mm, but beyond the insertion of the ductus arteriosus, the aorta widened again to its original width. Just proximal to the isthmus, the innominate, the left common carotid and the left subclavian arteries were normally given off.

The aortic ring had three semilunar cusps, a right, an anterior and a posterior. From the posterior sinus of Valsalva sprang the right coronary artery running to the sulcus longitudinalis posterior. Thus the posterior cusp corresponded to a normal right one. Just to the left of and above the right coronary orifice, opposite the commissure between posterior and anterior cusps, was the orifice of the left coronary artery, which ran into the sulcus longitudinalis anterior. The anterior semilunar cusp thus corresponded to a normal left.

From the wall between the small aortic and the large pulmonic trunk, a short ridge extended into the ventricular chamber toward the anterocranial edge of the septum. This prolongation of the aortopulmonary septum toward the interventricular one closed part of the latter's defect. It reduced somewhat the communication between right ventricle and pulmonic trunk. The aortic trunk thus

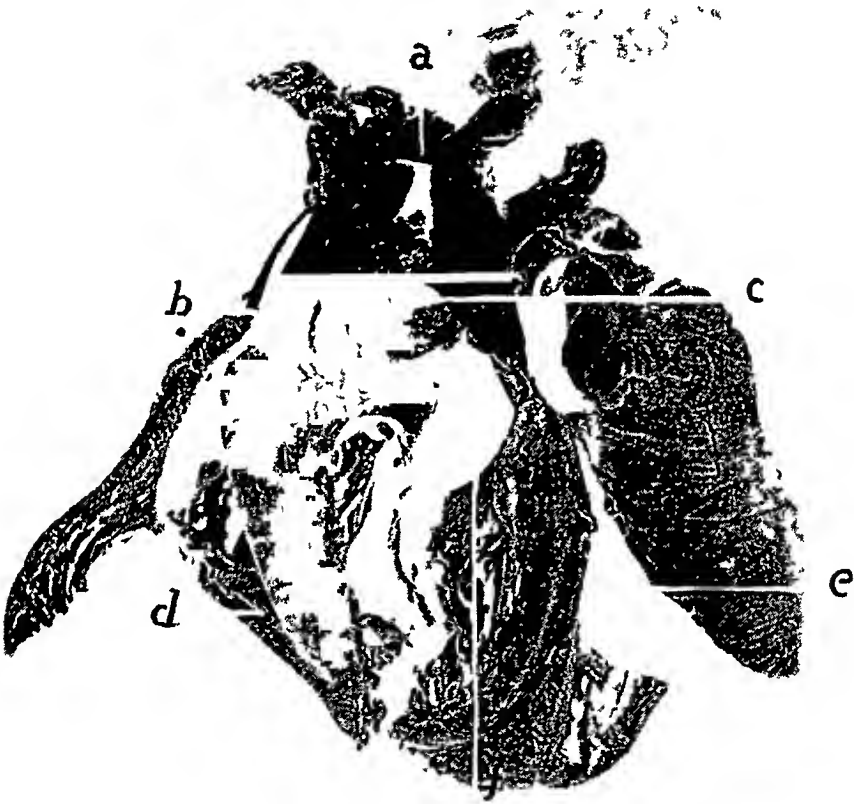


Fig 5 (case 3) —Deformity of the heart viewed from in front. The letters indicate *a*, ductus arteriosus, *b*, aorta, *c*, pulmonic trunk, *d*, right ventricle, *e*, left ventricle and *f*, defect of ventricular septum.

drained entirely from the right ventricle, the pulmonic from both, but mostly from the left ventricle.

The atria were normal, except that the left auricle was much larger than the right. The great venous trunks and the atrioventricular orifices were also normal.

Summary—As congenital defects in this heart, there were, therefore

- (1) Incomplete transposition of the great arterial trunks (detorsion defect)
- (2) Hypoplasia of the aortic trunk, especially at its isthmus
- (3) Patent ductus arteriosus
- (4) Interventricular septal defect
- (5) Hypertrophy and dilatation of the left cardiac chambers

ANALYSES

These arrays of cardiac abnormalities merit analysis, as far as recent conceptions of the mechanism of cardiac embryology can carry it. One separates from the changes secondary to intra-uterine endocarditis, those which, as in the present cases, arise from a primary deficiency in *vis a tergo*. There is a diffuse weakening in the growth vitality of various cell groups. These proceed lamely to form their appointed structures. They fall short of completion.

But in this regard, one cannot consider the congenital defects as simple cessations of development. The congenital heart of a "blue" baby at term is not, for example, the heart of a normal fetus of the second month. For its various parts are growing at different speeds. And further, these primary delays in development give rise to such alterations of fetal cardiac physiology that the normal channels of growth are deflected from their course. Abnormalities arise, therefore, which have no counterpart in the normal heart or at best offer only a vague resemblance. Structures appear which should have completely involuted. Defects arise by failure of normal completion. Still other defects represent the secondary involution or the deflection of structures normally formed. All these must be sharply distinguished.

Decrease in growth vitality presumes some cause. This is to be found often in the exhaustion of multiple pregnancies. The first child was the last of a line of five, the second was the youngest of a line of nine children. All the previous children in each family were normal, the last ones were not quite fully equipped.

The deficiency is generalized. It is manifested not only in one organ, but here and there all over the body. The defects in the heart in the first case were accompanied by a complete aplasia of the spleen. Those in the heart in the second case were associated with polycystic kidneys, mongoloid idiocy and bilateral coloboma of the iris.

The heart in the human embryo of 2 mm. forms an unpaired tube suspended in its pericardial chamber. As it grows faster than the cavity in which it lies, it buckles to the right. It bends more and more until finally it bends into a complete circle in which the original caudal or atrial end comes to lie behind the original cephalic or bulbar end. With this bending, a complex longitudinal clockwise torsion takes place.

For the bending and the torsion, Spitzer¹ advanced this concept. In lung-breathing animals, according to him, the basis of cardiac development is the division of the organ into a double heart. In gill-breathing aquatic animals, the heart is single, with the respiratory and systemic parts lined up one behind the other, and with septums transverse to the stream. Terrestrial life and lung breathing bring a requirement for greater systemic energy and for an even far greater respiratory energy. The whole heart grows even beyond its original limits. It must therefore bend.

This increase in development is not uniform. The relatively greater respiratory energy required with lung breathing gives a relatively greater development to the pulmonary part of the cardiac tube. As it begins to compare with the systemic part, it lines up beside the latter, so that the two parts, instead of being one behind the other, are side by side.

The transverse septums melt under the increased force of blood flow. At first the systemic force is so much greater than the pulmonic that the two streams partly mix and septal development between the two parts of the heart is impaired. Such are the conditions of the incompletely divided hearts of amphibians and reptiles. With the relatively greater pulmonary development in mammals, the force of the pulmonic blood flow approaches that of the systemic. The streams no longer admix. Where they flow by each other, the pressure is least, and longitudinal septa are permitted to develop. When other factors disturb the equalization of pressure, septal defects develop.

The right side of the heart is separate from the left. Were it, however, a simple division, one side would be completely cut off from the other. Blood to the right side of the heart would be aerated by the lungs, and go in an endless cycle directly back to the right side. Blood to the left side of the heart would course through systemic channels and return unaerated to the left side, with never an exchange. Therefore, there must take place a complete, 180 degree torsion of the arterial end so that aerated pulmonary blood may go to the left side of the heart and be discharged therefrom, while nonaerated systemic blood goes to the right side of the heart and is discharged into the lungs. That such a rotation occurs is seen in the clockwise spiral of the aortopulmonary septum. Thus, in the definitive heart, as the pulmonic trunk descends it swings from behind the aorta around to the left and anterior, reversing, proximally, its distal relation to the aortic trunk.

On this theory, when the fetus is insufficiently endowed with vitality in vascular growth, these processes of cardiac development are not consummated. The pulmonic side usually suffers first and most. Normal development and normal involutions are impaired. Septal formation is defective. Torsion occurs incompletely or not at all, so that the so-called detorsion defects develop. The whole picture is finally clouded by the secondary changes arising from the alterations in fetal cardiac physiology.

In my first case, the single arterial trunk issuing from the hypertrophied left ventricle was guarded by an anterior, a right and a left semilunar cusp, whereas it should normally have presented a posterior, a right and a left cusp. That there had been a complete absence of the 180 degree clockwise spiral rotation was also proved by the reversal of position of the coronary arteries. That arising from the right cusp

corresponded in distribution to a normal left coronary artery. That arising from the left cusp had the normal distribution of a right coronary artery. One had here a complete, or 180 degree, detorsion defect.

I do not consider the single arterial trunk as a true, persistent truncus communis arteriosus. In the original truncus communis, four proximal endocardial buds develop. Fusion of the apposing larger pair forms the aortopulmonary septum. But in forming the septum, the pair of large buds is divided into four. These, with the undivided pair of small apposing buds, make a total of six from which six semilunar cusps develop. If a single arterial trunk is really a persistent truncus communis, the proximal large pair of buds do not fuse. The septum fails to develop, and the buds are not divided. The single arterial ring is left with four endocardial swellings to form four semilunar cusps. Thus von Huelse³ points out that a single arterial trunk may be considered a true truncus communis only if it has four semilunar cusps. Only two such cases have been described, one by Preisz⁴ and one more recently by Santa Cruz⁵.

If the large pair of endocardial swellings do fuse, the resulting septum divides the truncus into two vessels with six buds giving six semilunar cusps, three for the aorta and three for the pulmonary artery. This is the normal definitive state. But if the aortic or pulmonic side subsequently disappears, the single arterial trunk remaining would have only three semilunar cusps. Thus, if a single arterial trunk has only three cusps, it cannot be considered a true truncus communis. It must be held simply as a truncus solitarius, either an aorta or a pulmonary artery, with complete involution of its fellow.

That the single arterial trunk in my case¹ was an aorta is certified by the normal origin of both coronary arteries, as well as the great vessels of the head and upper extremities, from it. In cases of hypoplasia of the aorta, one or the other coronary artery has occasionally been described as found in the pulmonary trunk, but never both. In these cases, too, the pulmonic trunk continues into the descending aorta by way of a patent ductus arteriosus, and the great vessels of the head and arms have an anomalous origin.

In cases of single arterial trunk with three cusps, Monckeberg² could find not even a histologic trace of a pulmonary artery. Von Huelse regarded these as cases of complete involution of the sixth (pulmonary) embryonic arch. The lungs are then supplied by bronchial arteries, by a persistent ductus arteriosus or by anomalous branches from the great vessels of the neck.

3 Von Huelse, cited by Monckeberg (footnote 2)

4 Preisz, cited by Abbott, Maude. *Osler's Modern Medicine*, Philadelphia, Lea & Febiger, 1925

5 Santa Cruz, J. Z. Common Ventricular Opening for Aorta and Pulmonary Artery, *J. Philippine Islands M. A.* 5 295 (Oct.) 1925

The deficiency in the growth vitality of the pulmonary vascular elements reflected itself in several other abnormalities. The right or pulmonary ventricle was an insignificant vestige. The interventricular septum had been unable to reach its full height, and left a large interventricular defect above it. It was pushed over against the right lateral wall of the almost single ventricular cavity, and buried under the incompletely evolved tricuspid valve.

The auriculoventricular valves form, as do the semilunars, from four endocardial thickenings, two of which are split by the division of the heart. This gives six valve rudiments, each with a group of chordae tendineae. Normally, the left lateral and anterior buds, failing to divide, form the large bicuspid leaflet of the mitral valve with its two groups of chordae tendineae. A similar fusion occurred in my case between the left lateral and posterior buds to form the large leaflet that hung into the cavity of the left ventricle. But the whole tricuspid valve rudiment had also failed to divide. A single large leaflet with three groups of chordae remained on the right lateral wall of the ring. It represented all three of the tricuspid valve leaflets, and curtained the entire right ventricle.

The completion of the ventricular septum was inhibited. Normally, it is effected by a union of the two large endocardial cushions at the base of the ventricle. This divides the auriculoventricular orifice into right and left parts. With this as a keystone, closure is consummated by a union with the septum primum atriorum growing down from above, with the interventricular septum growing up from below, and with the prolongation of the aortopulmonic septum extending backward from the anterior upper corner. This anterior portion was present in the anterior ridge described extending from the right wall of the single arterial trunk toward the ventricular septum. The presence of this trace of septum aortopulmonale is further proof for our contention that the original truncus communis had once been completely divided, and that the pulmonary side had involuted.

The large endocardial cushions, the keystone of the division, had failed altogether to develop. The interventricular septum had been unable to reach its usual height. The septum primum atriorum had not grown down far enough. Thus a large defect was left between the ventricles, and the auriculoventricular orifice remained undivided.

A similar retardation of development was suffered by the septum atriorum. The septum primum atriorum had developed. Normally, its inferior edge forms, with the endocardial cushions, a foramen primum, which is closed later by the completed growth of the septum. Absence of this closure left a persistent foramen primum. Normally, the septum primum then develops a large defect in its craniodorsal region, the foramen secundum or ovale. This is closed by the valvelike down-

growth of a septum secundum just to the right of the first septum. A large foramen ovale formed in my first case. It was denied closure, however, by the absence of a septum secundum. This reduced the interatrial septum to a narrow band stretching across and above the common auriculoventricular orifice, with a persistent foramen primum below and a large persistent foramen ovale above.

The network extending from the right margin of the coronary sinus to the crista terminalis, known as rete chiari,⁶ is the remains of the right valve of the sinus venosus. This valve definitely forms the thebesian and eustachian valves. It unites at the crista with the left valve of the sinus venosus to form the septum spurium. This left valve in my case was absent. Chiari's nets are not infrequent deformities.⁷ Twenty-six cases have been reported. Two other cases were but recently found by me in adult otherwise normal hearts.

The general decrease in the growth energy of the heart is seen also in the failure of the left atrium to take up the pulmonary vein in its wall. This vessel is absorbed normally until its second branching is reached. Thus four pulmonary veins come to enter the atrium. No such absorption occurred in my case, the pulmonary veins entered by a single venous trunk.

Clinically, a dextrocardia was diagnosed. The apex was on the right side. But one must distinguish between a situs inversus and a dextroversio cordis. The first represents a mirror image of the normal. The second is simply a shifting to the right of the cardiac apex. The normal left position of the heart is determined by two factors. First is the descent of the heart in the thorax. If this fails, as in ectopia cordis cervicalis, the apex is in the midline. Second is the upward growth of the predominant right lobe of the liver. This pushes the apex to the left. When the left lobe of the liver is abnormally relatively large, as it was in my case,¹ the cardiac apex is pushed to the right. Thus arose the dextroversio cordis.

Absence of the spleen was associated with a tremendous giant cell response in the tuberculous abdominal lymph nodes. Dr R. H. Jaffé, in a personal communication to me, pointed out just such a response in animals which after splenectomy had been infected experimentally with tuberculosis.

The second case requires little additional comment. It comprises a somewhat less extensive congenital upset than the first. The common coronary artery represents a fusion of the right and left endocardial buds so that only two semilunar cusps remained to the aorta. The single coronary artery partook of the features of both vessels. It pos-

6 Chiari, H. Net Formation in the Right Atrium of the Heart, Beitr. z. path. Anat. u. z. allg. Path. **22** 1, 1897.

7 Jordan, W. R. Chiari's Network, Arch. Path. **2** 840 (Dec.) 1926.

sessed the anterior descending branch of the left, and the right circumflex branch of the right coronary artery

Cases in which the aorta, somewhat dextroposed, rides over a ventricular septal defect, receiving blood from both ventricles, are not uncommon. Usually in these, there is an atresia or stenosis of the pulmonary artery as in Roeder's⁸ case and in Zimmermann's.⁹ Occasionally, the pulmonary artery is the main vessel, as it was in my third case. A complete dextroposition, however, with both trunks, separate and equal, arising entirely from the right ventricle is rare. The left ventricle can discharge its blood only through the interventricular septal defect.

Previously this defect was explained in the following fashion. With stenosis of one vessel or the other, septal defects arise and the greater the stenosis the greater is the defect. Septal defects, unless small, cause such an alteration in pressure relations between the two chambers, that their normal developmental relations are altered. One enlarges at the expense of the other. In my second case, the right hypertrophied, and as it grew pushed the ventricular septum to the left. This left the aorta behind in the right ventricle.

Since in my case there was no stenosis of either trunk, it is simpler to apply Spitzer's detorsion theory. The aortic dextroposition would then represent simply a failure to complete the last stages of torsion. As the aorta in front and the pulmonary artery behind swung clockwise around each other to bring the latter anteriorly, the aorta had rotated posteriorly but not enough to the left to reach its appointed place in the left ventricle. Thus, the aorta instead of being, as it is normally, almost directly behind the pulmonary artery, was posterior but to its right. The clockwise torsion had not completed its 180 degrees, but only about 120 degrees. One had, then, in the second case, simply a 60 degree detorsion defect.

The aorta lagging behind in the far right corner of the right ventricle received but a part of the right ventricular discharge. The pulmonic trunk in its more central position close to the ventricular septum received, not only the rest of the blood of the right heart, but also most of the blood of the left ventricle, which was coming through the septal defect. This elevated the pulmonic pressure above the aortic, and kept the ductus arteriosus patent, to neutralize the difference.

As mentioned, cases of dextroposition of the aorta are not rare. The third case was, however, a direct reversal of such an anomaly. It was, in effect, a sinistroposition of the pulmonic trunk. The pulmonic artery had been shifted to the left and straddled the septum so that it

⁸ Roeder, O. J. Complete Obliteration of the Pulmonary Artery, *J. A. M. A.* **79** 16 (July 1) 1922.

⁹ Zimmermann, H. M. Truncus Arteriosus Communis, *Am. J. Path.* **3** 617 (Nov.) 1927.

belonged almost entirely to the left ventricle, but partly also to its proper ventricle, the right. The ventricular septal defect helped to maintain its communication with the right ventricle, but this was reduced by the prolongation of the septum aortopulmonale. This swung down from between the great trunks toward the ventricular septum to close the anterior corner of the defect. The aortic trunk was misplaced in the opposite direction. It was to the right of the pulmonic, and issued entirely from the right ventricle. Instead of being, as normally, posterior to the pulmonic trunk, it was anterior to it.

This almost complete reversal of the relative positions of the two trunks may be readily explained as the result of incomplete torsion. As the pulmonic and aortic trunks, the first directly behind the second, began to rotate clockwise around each other, they were stopped in the earliest stages. The pulmonic had moved a little to the left and anteriorly, the aortic a little to the right and posteriorly. About 60 degrees of torsion had been affected, and there torsion stopped, leaving each arterial trunk still in its wrong ventricle. One had then, in this case, a detorsion defect of about 120 degrees.

So one finds, in confirmation, that the semilunar cusps in each great trunk had shifted their positions part way around the circle. The pulmonic trunk should present an anterior, a right and a left cusp. In the case in question, it presented a left, an anterior and a posterior cusp. The aorta should have a posterior noncoronary and a right and a left coronary cusp, it had a right noncoronary and a posterior and an anterior coronary cusp.

The pulmonic trunk enlarged because it drained the entire left ventricle and part of the right. The aorta was hypoplastic because it received only part of the flow from the right ventricle. The pulmonic excess spilled over into the aorta by way of the funnel-shaped patent ductus arteriosus.

This third case stands between the first and the second. The first represented a detorsion defect of 180 degrees. In the second, torsion had been almost entirely completed, so that we had only a defect of 60 degrees. In the third, it had only been begun, giving a detorsion defect of 120 degrees.

CONCLUSIONS

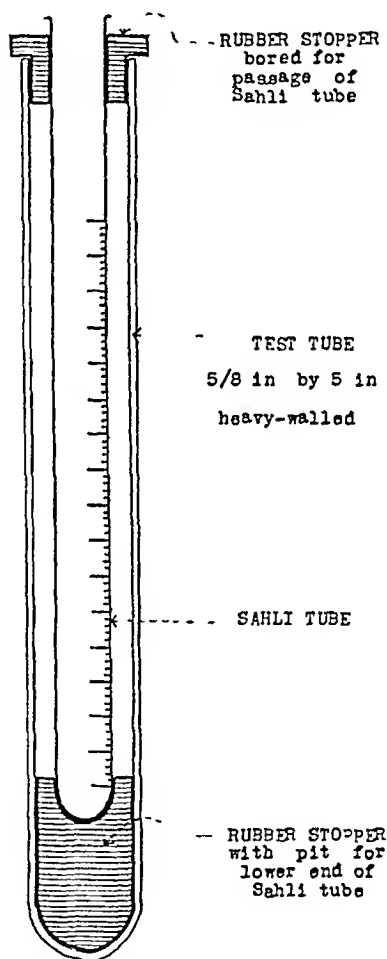
The puzzling picture presented by three cases of complex congenital cardiac anomalies have been analyzed as primarily based on detorsion defects. The three cases express different degrees of the anomaly. The first was a complete, the second a slight, and the third an intermediate, detorsion. Other defects were simply associated ones in the deficiency of vitality in vascular growth, or were secondary to the changes imposed by the detorsion.

Laboratory Methods and Technical Notes

A HANDY DOUBLE-PURPOSE HEMATOCRIT

O B PRATT, M D, AND H O SWARTOUT, M S, LOS ANGELES

Having had frequent occasion recently to test blood both for the per cent by volume represented by the cells and for the carbon dioxide-combining power of the plasma we developed a simple piece of apparatus



Double-purpose device for testing blood

which has proved very convenient. As it may at times be useful to others we describe it here.

For materials, one needs only a $\frac{5}{8}$ by 5 inch heavy-walled test tube, rubber stoppers and a graduated tube of the kind used in Sahli hemoglobinometers. The use of Sahli tubes for such a purpose is not a new idea, but we have not elsewhere seen a method of mounting similar to ours.

* Submitted for publication, Oct 19, 1929

* From the Research Laboratory of the White Memorial Hospital, College of Medical Evangelists

The details of construction are shown in the accompanying diagram. The rubber stoppers are readily shaped with the aid of a cork borer and a pocket knife. The one in the bottom of the test tube fits snugly enough to prevent its falling out when the tube is inverted. The upper one is fitted water tight. The flange on this stopper prevents it from forcing itself down into the tube during centrifugation. The device does not need to be taken apart for cleaning, and we have been troubled but little with breakage.

We take blood by venipuncture, oxalate it and after careful mixing, pipet from 2 cc. to 2.5 cc. into the inner tube of each of a pair of these devices, we then centrifugate the preparation at high speed until there is no further noticeable diminution in the volume occupied by the cells. The upper levels of both cells and plasma are easily read on the scales of the Sahli tubes, the per cent by volume represented by the cells being calculated from the averages of the values thus obtained. The clear plasma is then pipetted off for use in the determination of its carbon dioxide-combining power in the regular way.

General Review

THE INTRACELLULAR "SYMBIONTS" AND THE "RICKETTSIAE" *

R W GLASER, D Sc
PRINCETON, N J

Certain investigators have been interested for years in the so-called intracellular "Symbionts" and "Rickettsiae," limited in their dispersion among vertebrates, but widely disseminated among invertebrates. In the latter animals, the micro-organisms are ordinarily regarded as innocuous parasites, commensals or true symbiotic forms, which live in a state of mutualism with their hosts. A symbiotic relationship is usually assumed, especially by workers on the more strictly biologic aspects of the subject. This attitude is founded principally on two generalizations: (1) the adaptation between the invertebrate and the invader has, in most cases, reached a marvelous degree of perfection, manifested by many morphologic and physiologic accommodations on the part of the host, and (2) the transmission of the micro-organisms to succeeding generations through the eggs of every individual of the species has been established in a remarkably orderly, though as yet unaccountable, manner.

Some of the micro-organisms in question, through the bites of their arachnid and insect hosts, gain an entrance into the vertebrate body, where they either are destroyed or manage to survive, although inhibited to such an extent that no injury results. Others appear to be adapted to the vertebrate as well as, or better than, to the invertebrate host, and cause serious diseases among men and domestic animals. In these cases of pathogenic effect, the parasites seem to be losing their perfect adaptation to the invertebrate host, for every individual of the species is not infected and, with one exception, transmission through the eggs has been abandoned. Neither the taxonomic status nor the food habits of the hosts can be correlated with the presence or absence of infection by "symbionts"; they occur within a great variety of totally unrelated forms, within blood-sucking and nonblood-sucking forms, within plant juice-sucking forms and within carnivorous, herbivorous, coprophagous and omnivorous species.

* Submitted for publication, May 31, 1929

~ From the Department of Animal Pathology of the Rockefeller Institute for Medical Research

It seems at this time advantageous to present a critical review for the purpose of assembling the most important matters, and to point out certain relationships and problems that have not been sufficiently emphasized. The literature on the intracellular "symbionts" and "ickettsiae" is extensive, for this reason, I may neglect a number of minor facts and points of view. Also a few papers remained inaccessible to me, and in these instances the citations of other authors have been accepted. Restriction will also be practiced for the sake of concentration on a circumscribed group of problems that appear interrelated. It is impossible at this time, for instance, to discuss fully the interesting relationships that exist between unicellular algae and certain protozoa, sponges, coelenterates and worms. It is also deemed advisable to omit a discussion of the interesting cecal bacteria of certain heteroptera described by Glasgow (1914), and the micro-organisms found in a peculiar organ situated in the connective tissue of certain operculate land mollusks, fully treated by Meyer (1925). The remarkable cases of extracellular symbiosis, as exemplified by Cleveland's work (1924, 1925) on the protozoa found within the alimentary tract of termites, will be only briefly treated because they do not appear to come within the scope of this review.

THE INTRACELLULAR "SYMBIONTS"¹ OF INVERTEBRATE ANIMALS

THE "PSEUDOVITELLUS" AND "SYMBIONTS" OF APHIDS

The subject of intracellular symbiosis in the higher invertebrates had its inception in an observation by Leydig (1850), who found green, yellow or brown granular masses within the blastoderm stages of certain viviparous aphid embryos. To Leydig, these masses appeared to lie free between the cells and later were converted into large spheres which became enveloped by membranes and participated in the development of the reproductive organs of the insects. Huxley (1858) described the structure in adult aphids and considered it an organ of inconstant form constructed of cells that enclosed yolklike spheres. To this author, the spheres were identical with the true egg yolk and he derived the fat body from them. Lubbock (1859) concurred with Huxley. Metschnikoff (1866), during his embryologic studies of *Aphis rosae* and *pelargonii*, had his attention attracted to a particular cell that occurred in the germinal invagination at the time of the formation of the blastoderm. This cell, which measured approximately

¹ Portier (1918) and Meyer (1925) called attention to the fact that "symbiont" is a misnomer, the Greek word for "companion" or "partner" being "simbiote." Common usage, however, has soundly established the word "symbiont" unfortunately, so it will be retained throughout this discussion for the sake of preventing confusion.

0.013 mm in diameter, contained, in contradistinction to the other cells, greenish or yellowish granules. It divided and formed a number of greenish or yellowish cells, which *en masse* separated from the remaining cells of the germ. Balbiani (1866) also studied the structure and found that the rapidly dividing cells formed a voluminous organ that remained in close proximity to the developing reproductive system of the embryo. This writer named the organ in question the "pseudovitellus," a name which has only recently been replaced by a more appropriate one (mycetoma or mycetome). Balbiani investigated the embryology of winter forms, in which phenomena occur somewhat different from those observed within the ova of viviparous females. He stated that within oviparous females a small follicular cell grows toward the ovum until the two touch, then a fusion occurs. The follicular cell, however, does not lose its identity, but becomes deeply embedded within the egg yolk, while anchored to the follicular epithelium by means of a delicate stalk. Later, the portal of entry into the blastoderm closes and the stalk is absorbed. Thus Balbiani traced the origin of the "pseudovitellus" in certain aphids. The observation, if correct, is remarkable, because it constitutes a case of the inheritance of certain characters through somatic cells. It is now well known that in many forms the "pseudovitellus" persists through embryologic development and with certain modifications maintains its identity even in the adult stage, but whether transmission of an entire somatic cell to the next generation occurs in aphids, in the manner described by Balbiani, remains in doubt. Subsequently, "pseudovitelles" were found at the posterior pole within the eggs of certain cicadidae, cercopidae, psyllidae, aleyrodidae, aphididae, coccidae, etc., by Heymons, Porta, Pierantoni, Sülc, Buchner and others. Pierantoni (1910) and Sülc (1910), independently, discovered that all these organs harbor micro-organisms that morphologically resemble in some cases either fungi or yeasts, in others bacteria.

Buchner (1912, 1919), Uichanco (1924) and Klevenhusen (1927) contributed many details in their studies of aphids that lead toward a better understanding of the "pseudovitellus" and its contents. Buchner designated the "pseudovitelles," "mycetomas" or "mycetomes," and the individual cells of which they are composed, "mycetocytes." The inhabitants of the mycetocytes were called "symbionts" by Buchner and all other recent workers. In the parthenogenetic form of the aphid *Macrosiphum tenacetis*,² Uichanco found two relatively large mycetomas in the abdomen. After birth the component units, or mycetocytes,

² *Macrosiphum tenacetis* L. was used primarily because it belongs to Aphidinae, one of the most primitive subfamilies of Aphididae. Hence better prospects existed to observe characters that might otherwise be modified, obscured or lost as a result of specialization.

apparently cease dividing. They, nevertheless, increase in size from about 42 to 45 microns, in the first instar, to about 72 to 108 microns in the adult. After the insect has matured, these cells begin to degenerate slowly until the end of the aphid's life, when only a few remain. Buchner also found the cells of the mycetomas in *Diepanosiphum platanoides* large and possessing a correspondingly large nucleus, which usually contains a nucleolus. Both Buchner and Uichanco never found the nuclei invaded by the symbionts. Indeed, the immunity of the nucleus toward invasion has been observed by all workers in this field. In aphids, the cytoplasm of the mycetocytes is filled with large micro-organisms that resemble the yeastlike forms of certain fungi, but such heavily beset cells never show degenerative nuclear changes. It has always been a marvel to me that such cells, packed with foreign bodies, can exist at all. The symbionts themselves possess nuclei, and the figures of nuclear division have been observed in some of them. Fission, and not budding, represents the usual method of reproduction within the host. Variations in size of the fungi occur in separate mycetocytes, the round form investigated by Buchner measures between 2 and 4 microns in diameter. Occasionally, mycetocytes occur that do not possess a definite membrane. Such cells are in the act of discharging a portion of their inhabitants into the blood, where free individuals are sometimes found. Mycetomes and mycetocytes, with specific inhabitants, occur in every individual of a particular species of aphid whether amphigonous, male, female or parthenogenetic. A particular symbiont is always host-bound (exception: symbionts of mites), the same form is never found within different host species. Two or three distinct species of symbionts are, however, often found within one host. This universal infection is primarily due to the fact that transmission from generation to generation has been established through the eggs. Males also harbor mycetomas and mycetocytes with residents. The organs seem to bear a close topographic relationship to the testes, but entrance of the symbionts into the spermatocytes and spermatozoa has never been observed. For this reason, transmission of symbionts by the male is highly improbable. The transmission occurs only through the female, and in this manner simulates a sex-linked inherited character.

In viviparous aphid females, Buchner (1919) found that the egg prepares itself prior to infection. The posterior section of the blastoderm of the embryo separates from the rest and temporarily fuses with the surrounding follicle cells. At this time, the fungi are found within certain ovarian tubule mycetocytes. The surface of one of these mycetocytes dissolves and the fungi pass over into the specially prepared blastoderm cells. The invasion continues slowly and ceases when the embryonic cells mentioned have become entirely filled. Later,

the invagination of the germinal streak occurs at this point, and the fungi are carried into the interior of the embryo. The embryonic cells containing the symbionts constitute the embryonic "pseudovitellus" or mycetome. The foregoing interpretation by Buchnei may be also the correct one for Balbiani's work, in which he derived the "pseudovitellus" from a follicular cell and described its passage into the egg of certain oviparous aphids.

In the parthenogenetic females of *Macrosiphum tanacetii*, and some other aphid species, Uichanco also found symbionts within certain cells of the ovarian follicular epithelium, where they multiply rapidly and produce some swelling of the follicle adjoining the posterior pole of the enclosed egg. The micro-organisms break through the thin epithelial cells and invade the posterior pole of the egg through a posterior opening in the periplasm. The vitellophags, which Uichanco now calls "mycetoblasts," are attracted to the micro-organisms and congregate around and between them in the posterior half of the egg cavity. This attraction of the "mycetoblasts" to the invaders simulates the behavior of leukocytes in the presence of foreign material (phagocytosis). The "mycetoblasts," together with the egg cytoplasm with which they are in syncytium, and the enclosed symbionts, form a subglobular mass. In this manner, the anlage of the "pseudovitellus" is established. Cellular differentiation of the anlage occurs after active mitotic division of the mycetocytes, shortly before the metameric segmentation of the germ band. After differentiation of the organ, the cells divide at least once during the embryonic stages of the aphid, increasing in number from about thirty or forty to about sixty or seventy. After birth, the cells do not divide and the entire organ measures approximately from 1 to 2 mm in diameter. On birth, the organ is represented by a single mass of "mycetocytes," but later this mass divides into two lateral halves, apparently as a result of pressure exerted by the developing digestive tube. At about the fourth instar of the parthenogenetic female, the mycetome becomes reduced to isolated groups of two, three or more "mycetocytes," as a result of compression by the overcrowded and continually growing embryos within the mother. At this stage, the cells are larger, showing an increase from 42 or 45 to about 72 or 108 microns in diameter. The organs were found by Uichanco to be well supplied with large tracheoles.

Within oviparous females the situation varies again, as shown by Buchnei for *Drepanosiphum platanoides*. After the nutritive nurse cell strands have been absorbed and the lumen of the ovarian tubule has closed anteriorly, separating the developing ovum from its successor, invasion by the fungi occurs. Individual fungi appear between the spaces in the follicle and the peritoneum, and are attracted by and penetrate the surface of the ovum, which invaginates a bit to receive

the invaders. The invasion of the ovum continues for some time, and the symbionts move anteriorly within it as if to make room for the succeeding individuals. The penetration of the fungi cannot alone account for all found within the ovum at this stage, active multiplication of the symbionts must also play a part. The wandering or invading forms appear slightly different from the resting forms within the mycetocytes of the adult. From the published figures, they seem longer, and many dividing individuals are evident. The fungi are later observed within the blastoderm, but the establishment of the embryonic mycetome of the oviparous female has not been traced. It apparently occurs in *Drepanosiphum platanoides* in a manner similar to that described by Buchner for the parthenogenetic females of the species, or to that described by Uichanco for *Macrosiphum tanacet*.

Klevenhusen (1927) described cases of monosymbiosis, dysymbiosis and trisymbiosis in aphids, or infection of the insects and their ova by one, two or three distinct micro-organisms. This writer suggests mechanisms to explain partially the sortings, migrations and orderly arrangements of the micro-organisms within the eggs and embryos. He finds that the relationships are simpler in the primitive aphids than in those more highly specialized. So-called primary symbionts are found in all aphids. These differ from host to host, but they are invariably found, are never degenerate and are located within mycetomes. These primary forms are considered the more ancient phylogenetically because they seem perfectly adapted to their hosts. The secondary forms often show degenerating individuals, and are elongated, rod-shaped or sausage-shaped. These are not so well localized and may occur free within the body cavity, within blood cells, connective tissue cells and oenocytes or within syncytial cell masses (primitive mycetomes or mycetocytes). Klevenhusen assumes that the secondary forms entered on the symbiotic relationship during more recent times, because their adaptation to the hosts is less marked than that of the primary forms.

THE MYCETOMAS³ AND SYMBIONTS OF THE CICADIDAE, CERCOPIDAE, PSYLLIDAE, ALEYRODIDAE AND COCCIDAE

Within *Cicada* *oim*, according to Buchner, conditions are complicated. This insect is dysymbiotic, i.e., it possesses a mycetome and also unconcentrated mycetocytes that are really certain cells of the fat tissue. These mycetocytes harbor a totally different fungus from the one enclosed within the mycetome. This fat body fungus was named *Saccharomyces cicadarum* by Sölz, and although the lymph appears free the symbiont is capable of wandering around among the various fat

³ The term "mycetoma" or "mycetome" has now entirely replaced the older term "pseudovitelus."

cells. Some of these cells are filled with *Saccharomyces cicadatum*, others contain only three or four individuals. The mycetome of this insect is constructed of an epithelial outer layer of cells and an inner zone of morphologically different ones. A fungus occurs in the inner zone of cells immediately under the epithelial layer. This micro-organism has a totally different aspect from the one found within the fat cells.

Infection of the ovum begins after certain yolk preparations. The fungi enter the follicle and then invade the posterior pole of the ovum. At this point, masses of the fungus species derived from the mycetome accumulate with a few of the fat cell individuals. Within the ovum, after maturation, a distinct round mass is found composed of the two systematically distinct invaders, which segregate later during embryologic development and follow separate courses.

In *Aphnophora salicis*, another disymbiotic insect, belonging to the *Cercopidae*, a mycetome exists constructed of an outer and an inner group of mycetocytes. Two invaders occur within this mycetome, the peripheral cells contain one, which morphologically resembles a bacterium, the inner zone contains another having a fungus form. In the sexually mature insects, a few symbionts are found free in the lymph and in females are transported to the ova by this medium. The follicular epithelium is also infected with both forms, and when the invagination at the pole of the ovum ensues, the symbionts enter. The symbiont mass, containing the two species, appears, then, as a round ball in mature eggs. Buchner (1922) found that although both symbionts enter at the same time they remain segregated within this ball.

Much the same conditions exist in the larvae of *Psyllidae*, in which the mycetome occupies a large part of the abdomen and is constructed of a peripheral and an inner zone of cells, each zone harboring a distinct species of fungus.

In some of the larvae of *Aleyrodidae*, which are monosymbiotic, Buchner (1912) found a paired mycetome of a yellow, yellowish-brown or yellowish-red color, containing a single symbiont. In male pupae, the organ grows and wanders posteriorly toward the testes, which it completely surrounds. In females, in which the mycetome is much larger, a parallel phenomenon occurs. The architecture of the psyllid ovaries corresponds to that of the coccid ovaries. The oviduct has many side branches which bear the ova and their nurse cells. The nurse cells and ova are not differentiated as in other forms, both possess propagative characters, in other words, the nurse cells, often found in synapsis, are really oocytes. The mycetome grows and moves posteriorly as in males, its mycetocytes invade the central portion of the ovary and everywhere fill the spaces between the fine ovarian tubes.

This is as far as the matter was traced by Buchner in 1912. Previously, Signoret (1867) had recorded that he found the yellow body within the ovum in later stages independent of the germinal streak. In 1919, Buchner resumed his observations on the aleurodids and discovered that entire mycetocytes with their residents wandered into the ova. These somatic cells maintained themselves a while before they lost their identity within the other embryonic cells. This observation is certainly suggestive of the one reported by Balbiani in 1866 for certain aphids.

In the coccids, which are also monosymbiotic, closed complexes or mycetomes are unknown. The fungi are found within certain fat cells and are transported around within the fat tissue and within the lymph. The invaded fat cells Buchner characterizes as facultative mycetocytes to distinguish them from cells that are obligatory, in other words, are predestined at an early stage to be used by the symbionts. Owing to the lack of restraint on the micro-organisms within the coccids, the former escape into the body fluids and may be encountered almost anywhere within the bodies of the insects. When the females mature, the fungi are found between the nurse cells and the ova. Each ovum invaginates at this point to receive the invaders and also emits protoplasmic processes which engulf them. Usually only a few symbionts, approximately fifteen, take part in this initial infection.

THE BACTERIOCYTES (MYCETOCYTES) AND BACTEROIDES (SYMBIONTS) OF THE BLATTIDAE AND FORMICIDAE

Blochmann (1887) was the first to appreciate the significance of the bacteria-like structures within the tissues and eggs of certain insects. Wheeler (1889) also found and correctly interpreted similar structures within the egg of *Blatta germanica*. Cholodowsky (1891) agreed with the interpretations of Blochmann and Wheeler. The elements are often referred to in the literature as the bodies of Blochmann. Blochmann emphasized the resemblance between bacteria and the structures discovered by him, and in 1892 expressed the opinion that they bear a symbiotic relationship to the insects in which they are found. Later authors, Cuénot (1892), Henneguy (1904) and Prénant (1904), doubted the bacterial nature of the Blochmann bodies and referred to them as bacteroides. Blochmann found that in *Blatta* and *Periplaneta* the central portion of single fat cell groups is filled with straight or bent rods, from 6 to 8 microns long, which divide by fission. Such cells are entirely filled and do not contain any fat or urate bodies as is the case with the other cells of the fat body. The nuclei of these cells are never obscured and appear perfectly normal. In *Periplaneta orientalis*, these cells form a row and are surrounded by one-layered fat cells. In *Blatta germanica*, several rows of these bacteriocytes traverse the fat tissue.

Blochmann observed that transmission of the bacteria occurs from one generation to another. In *Blatta*, the young ova in the ovary are free, somewhat older ones show a few on their surface. The bacterial rods multiply with the growth of the ova, so that at first they form a single-layer, later a several-layered row around the periphery. Blochmann found the rods only rarely within the periplasm. In mature ova and in recently oviposited eggs, the layer is broken, so that it appears as if the multiplication of the rods cannot keep pace with the growth of the eggs. A direct wandering of the bacterioides out of the host cells toward the ova, through the follicle cells, was not observed. During the development of *Blatta germanica*, the rods lie under the blastoderm, after its formation, i.e., within the egg plasma. From here, they penetrate more deeply and collect in the spaces formed by the flowing together of the yolk. While this phase of embryonic development proceeds, the entoderm still persists on the ventral side of the egg. When this grows dorsally, the bacterioides are located only on the inner side of the ectodermal fat body. They fill certain cells that penetrate this tissue, thus presenting the typical picture found in the adult animal.

In 1892, Heymons published some work on four species belonging to the genera *Blatta*, *Periplaneta* and *Ectobia*. He observed that in *Blatta* masses of the rods collect in the middle of the ovum at the time when the germinal streak begins to overgrow the yolk. In *Ectobia*, the rods are more numerous than in *Blatta*, but at first they are also scattered on the surface of the ovum. After the beginning of the formation of the germinal streak all the rods concentrate in the middle of the yolk. Thus, in contradistinction to *Blatta*, the remaining parts of the ovum remain entirely free of bacterioides. In this manner, a large spherical mass appears, which is augmented by yolk cells or vitellophags.

For a species of *Periplaneta*, Buchner did not trace the events in detail. However, in 1912, he observed that the young oocytes were free from infection. The larger ova showed each a number of rods at the surface, which were apparently derived from the bacteriocytes (mycetocytes) of the mother and must have wandered through the follicular membrane. Blochmann previously stated that he never saw the bacteria in the follicle cells of *Blatta germanica*. Buchner, however, found the bacterioides of *Periplaneta* not only extrafollicular, but also within the cells. As the ovum grows, the bacteria at the surface become much more numerous and form a closed layer around the periphery. A congregation of the micro-organisms composing this layer next appears at each pole and many rods are seen lying perpendicular to the surface of the ovum. According to Blochmann, the actual infection of the egg occurs late, since the bacteria first appear actually within the egg after oviposition. Buchner agrees with this view.

During the embryonic development of *Periplaneta*, Heymons observed the following facts. In young oviposited eggs, two principal bacterial concentrations are noticeable, one at each pole. The concentration at the posterior pole later shifts to a definite position at the posterior end of the germinal streak. At this place, the mass sinks into the yolk, and at the same time increases in volume owing to the multiplication of the vitellogophags that invade the mass of micro-organisms. The nuclei of the invading vitellogophags become larger than the nuclei of the outlying cells and divide amitotically. The whole concentration of bacteria and vitellogophags migrates forward through the yolk and fuses with the anterior concentration. After the embryonic overgrowth of the yolk the mass is found within the middle intestine. The bacteria now disperse centrifugally and in scores move toward the intestinal wall, while the vitellogophags degenerate. On reaching the intestinal wall, the micro-organisms penetrate the embryonic midintestine and reach the fat body where they enter certain cells, completely fill the cytoplasm of these, and consequently modify such cells morphologically and physiologically. In other words, they transform such cells into bacteriocytes.

From the outline presented, it is seen that in roaches infection from generation to generation is provided for by a series of definite events, apparently not as complicated as in some other cases, but interesting enough to stimulate even the most phlegmatic imagination. Many details in the chain of events are entirely lacking, and if known would undoubtedly assist much in the proper interpretation. However, a morphologic study, such as the one just described, can do no more than hint at underlying causes. How nonmotile elements are transported along definite, and in some cases, at least, rather sluggish, channels and find their way from the adult host cells to the immature ova and return is entirely unknown. One can postulate phagocytic and tropic reactions, as well as other things, between the bacteria and the various tissues involved, however, such speculations, while permissible and stimulating, do not constitute proof.

The situation in roaches is interesting from another aspect. These insects represent surviving members of an extraordinarily ancient group. Many extinct forms, with little change from the present ones, have been found in the carboniferous rocks. It would appear important to examine some paleozoic and mesozoic cockroaches, of which nearly 200 species have been described, in order to determine whether any evidences of former intracellular symbiosis or of actual parasitism exist. If such evidences survive, it would show the association to have already been established approximately 200,000,000 or 300,000,000 years ago, an important historical fact for parasitology and bacteriology. Paleontologists possess the necessary technic for making extremely thin

sections of fossilized material by a process of grinding, so that the determination outlined should certainly be attempted

Among ants, Blochmann (1887) found that the early ova of *Camponotus ligniperda* and *Formica fusca* contained small rods. At first, the follicle cells are filled with the micro-organisms, but later they leave these cells and collect and multiply at the posterior vegetative pole of the egg. Blochmann also found the rods in female larvae of *Formica* and *Camponotus*, so there can be little doubt that the general condition simulates that found among the roaches. Ants have not been recently used as material for investigations on intracellular symbiosis.

THE MYCETOCYTES OR BACTERIOCYTES AND THEIR INHABITANTS WITHIN BLOOD-FEEDING FORMS

The intracellular symbionts of blood-sucking forms have attracted much attention within recent years owing to the fact that they either are identical with micro-organisms known as "Rickettsiae," or are often sufficiently similar, in many respects, to make a differential diagnosis impossible [Noguchi (1926) and others]. A group of workers placed certain intracellular inhabitants among the symbionts. Another group relegated others to the "Rickettsiae" for wholly unnatural reasons. A separation of the intracellular yeast and fungus forms from the bacteria-like structures may be a perfectly natural taxonomic procedure, but why the intracellular bacteria-like micro-organisms found in arthropods are sometimes placed in the "Rickettsia" group and at other times not admitted seems incomprehensible. The reasons underlying such a separation, on close analysis, do not hold, because, as stated, they are unnatural and a true classification is not built on convenience, but on phylogenetic relationships. Some workers place the intracellular invaders of the bedbug and louse, etc., among the symbionts, others place the identical micro-organisms among "Rickettsiae." It must be recognized that the underlying biologic principles involved in these two artificial groupings are identical and that further progress in classification can only proceed by studying the detailed characteristics of the invaders and not solely the general reactions of the host. Are the pathogenic and nonpathogenic protozoa or the parasitic and nonparasitic nematodes classified as separate phyla, orders, families or genera almost exclusively because of size differences and on the effects they produce?

Since most of the literature on the intracellular symbionts has remained detached from that on the "Rickettsiae," I have treated them separately. By so doing, I feel that I have been enabled to do greater justice to each group of workers and thus more properly to emphasize the close relationships that exist than would be possible by the handling of the two fields as a single entity. From the standpoint of conservatism, the method adopted may also be commended because should

it be proved later that one or more of the "ickettsiae" are not related to any of the intracellular symbionts, the whole subject will not have to be entirely disentangled again

Work on the intracellular symbionts in blood-sucking forms probably had its inception in an observation by Schaudinn in 1904.⁴ This investigator found that species of *Culex* and *Anopheles* possess esophageal evaginations which are regularly filled with *Saccharomycetes*. The yeasts are also found within the midintestine of mosquitoes and, according to Schaudinn, are transmitted through the eggs. In 1914, Schaudinn thought that the yeasts aided the digestion of blood in mosquitoes and further attempted to show that the micro-organisms injected into the wounds by the insects, during the feeding act, were in reality directly responsible for the itching and for the subsequent development of wheals. Buchner (1922), however, also found and investigated the yeasts of mosquitoes, and showed that Schaudinn's conception concerning the pathologic effects of these micro-organisms was incorrect. Buchner discovered that he could obtain the same effect by subcutaneously or intradermally injecting into human beings extracts from mosquito tissues not containing the saccharomycetes, indeed, tissue extracts from species which do not suck blood and which do not harbor symbionts of any sort answered equally well. The phenomenon first investigated by Schaudinn is apparently a reaction produced by the toxic effects of insect proteins or their cleavage products.

Stuhlmann (1907) obtained some tsetse fly (*Glossina brevipalpis*) material from Koch and described symbionts that he considered protozoa in greatly enlarged cells of the midintestine. Roubaud (1919) studied the situation carefully and found that in the midintestine of *Glossina*, a zone exists in which the epithelial cells are from three to five times larger than their neighbors, extend far out into the lumen and form voluminous papillae. These special epithelial cells are filled with bacillary micro-organisms. The inhabitants or symbionts are liberated from time to time by the disintegration of the cells that enclose them, and can be found free within the intestinal lumen of all tsetse flies. The bacteria measure from 3 to 5 microns in length, are distinctly rod-shaped and often arched or flexed. Although the rods appear to multiply by transverse division, Roubaud thought that they were more closely related to the saccharomycetes because he also observed unequal division or budding. With this taxonomic interpretation, Buchner (1922) did not agree. The symbionts are found within the proventricular cells and within the intestinal lumen of the larvae of

4 Some observers claim that Koch first discovered intracellular micro-organisms in tsetse flies. Since no accurate account of this discovery has been recorded by Koch himself, I am inclined to think Schaudinn should receive priority.

Glossina, and were traced through the pupal stage to the adult. Roubaud did not with certainty find the symbionts within the eggs, but felt that they must be transmitted, because extremely young larvae are infected. This investigator also thought that the micro-organisms are in some way related to the physiology of digestion, and for this reason considered them symbiotic. Roubaud also recorded finding symbionts in other *Diptera*, namely, in *Lipoptena cervi* and in *Hippobosca equina*.

Buchner (1921, 1923) found a paired mycetome containing symbiotic bacteria in both sexes of the bedbug (*Cimex lectularia*). The organ is sharply circumscribed and oval, and occurs in the third abdominal segment to one side of the intestine near the reproductive organs. It is of the same color as the fat body and can readily be seen with a hand lens, measuring 5 mm long by 3 mm broad. The individual mycetocytes (bacteriocytes) are large polygonal, polynuclear cells, and their plasma is filled with rodlike micro-organisms and smaller round or oval bodies. On trituration, the mycetome reveals two types of rodlike bacteria. A few are thin, filamentous, motile rods, measuring from 3 to 7 microns long or longer, the others are shorter and non-motile, and appear to represent transition forms. Between all these rods, minute round or oval forms exist. These, as well as still other more highly refractive bodies, Buchner could not interpret. He also often encountered another bacterium-like micro-organism apparently distinct from the first. This was a thin, oval form, 3 microns in length, found within the mycetocytes, intestinal epithelium, fat, spermatocytes, nurse cells, germ cells, oviduct and receptaculum seminis. No injury results to bedbugs from their infection by any of the bacteria-like invaders.

The ovarian nurse cells become infected with the symbionts at an early stage. From these, they pass over into the immature ova with the secretory streams. Buchner, however, also found still earlier stages that as yet had no connection with nurse cells, infected. It seems, therefore, that the eggs of the bedbug receive their quota of symbionts in two days. This case is unique, for in all other recorded cases of symbiosis the ovarian nurse cells and nutritive secretory streams leading from them remain sterile.

In older ova, the symbionts congregate at the posterior end under the surface. During the formation of the blastoderm they infect some of the cells, and when the invagination of the germinal streak occurs, are found at the anterior end of this. Soon the infected cells and some of their parasite-free neighbors are separated from the epithelial layer of the germinal streak and the amniotic anlage. As aggregates of cells, they are forced anteriorly by the germinal streak, which is progressively sinking into the yolk. When the germinal streak bends

into the characteristic "S" shape, it also grows by these cell aggregates and leaves them behind. While this is proceeding, the symbionts multiply and form a definitely circumscribed mass enclosed within typical bacteriocytes. At this stage of development, the eggs of the bedbug are deposited. The mass then divides into halves forming two distinct organs or mycetomes, which sink into the region of the abdomen. The mycetomes increase in size with each instar. This does not depend on a multiplication of cells, but is caused by a progressive increase in the individual units due to several (from three to five) amitotically formed nuclei within each cell. The organs are well oxygenated through fine tracheae, which penetrate between the mycetocytes.

The first invader mentioned is also not entirely restricted to the mycetome and ovary. Buchner sometimes found the fat cells, the receptaculum seminis and the epithelium of the oviduct heavily infected. Conditions within the bedbug are complicated, and it is probable that several species of micro-organisms are involved. As will be shown later, the "tickettsiae school" apparently encountered similar difficulties.

Buchner (1923) also investigated another blood-sucking heteropteron, namely, the tropical conorhinid, *Triatoma megista*. In this insect, no mycetome was found, but rodlike bacteria were observed within the cells of the salivary glands. Within the parasitic larvae of *Gastrophilus equi*, however, a large mycetome richly supplied with tracheae was observed by this same writer (1922) in the posterior end of the body. This horse bot mycetome represents the largest one yet described, measuring 10 mm long by 7 mm broad. Its cells contain threadlike bacteria. The origin and development of the organ have not been studied, but in the sexually mature flies that do not feed, the organ is lacking. Hence, Buchner believed that a relation exists between parasitism by the fly and the presence of the organ. However, some of the symbionts must survive pupation in order to insure transmission to succeeding generations.

Sikora and Buchner independently (1919) discovered mycetomes and mycetocytes in lice. The genera *Pediculus* and *Phthirus* each possess an unpaired mycetome located within the midintestine on the ventral side. In *Pediculus humanus capitis* and in *Pediculus humanus corporis*, the human head louse and the human body louse, respectively, the mycetomes consist of small yellowish cell groups. These mycetomes are not in direct communication with the intestinal lumen, and the individual cells are inhabited by sausage-shaped and rod-shaped micro-organisms. *Haematopinus pliferus* is also endowed with an elongated organ near the intestine. Other species of *Haematopinus* studied do not harbor closed mycetomes, but possess single mycetocytes scattered over the entire midintestine embedded deeply between the

epithelial cells. The oviposited eggs of all lice contain symbionts located within the yolk at the posterior pole.

Miss Florence (1924) carefully studied the symbiont situation within *Haematopinus suis*, the hog louse, also previously investigated by Sikoia, Buchner (1919) and Hindle (1921). She found the symbiont of the hog louse approximately 1 micron in width and showing great variety in length. The mean length for the shortest forms equals 2.5 microns. They are gram-negative and resemble rods, clubs, pot-hooks and crescents. Short chains or rod-shaped bacterial forms are always present. This observer found the symbionts present in the louse throughout its life history, located in mycetocytes on the wall of the midintestine. A well developed mycetome is found in each oviduct of the females. Miss Florence found that the symbionts were transmitted through the eggs. She felt that a physiologic relation exists between the symbionts and the digestion of blood, for the following reasons: 1. The mycetocytes are found in the midintestine where digestion occurs. 2. The increase of the symbionts is mechanically controlled through the rupture of the mycetocytes and the escape of the micro-organisms into the intestinal lumen. 3. Careful provision for transmission to the next generation occurs. 4. There is high mortality and an inability to raise a second generation when the lice are removed from their natural host and fed on man. As an appendix to the last statement, it may be mentioned that Miss Florence succeeded in a few instances in rearing lice until mature on human blood. In such lice, she was unable to find symbionts within the stomachs or within the eggs taken from the oviduct and uterus of the female. A second generation of lice could never be reared on human blood.

So far as the physiologic relationship between the digestion of hog's blood and the symbionts is concerned, the first fact observed by Miss Florence is suggestive, and the second one on the mechanical control of the micro-organisms may possibly be significant. The connection between points 3 and 4, however, I do not understand. Careful provision for transmission of micro-organisms to succeeding generations is provided for in all cases in which this curious relation between insects and lower forms exists. The micro-organisms are often, in many forms, far removed from the alimentary canal and any of its adnexa. The high mortality and inability experienced in raising hog lice on a foreign food is a phenomenon often experienced among other insects that do not harbor symbionts and are bound to a specific type of nutriment. The disappearance of symbionts from lice fed on human blood may simply signify that what has been experimentally proved to be injurious to the host is also injurious to the adapted invader. The same type of argument may really be applied to the first and second points also. The conditions within the mycetocytes located in the midintestine near the

digesting blood proved an ideal environment, and for this reason the micro-organisms settled there. That conditions are actually extremely favorable, under the louse's normal food conditions, is manifested by the continued development of the micro-organisms to such an extent that the host cells harboring them rupture periodically.

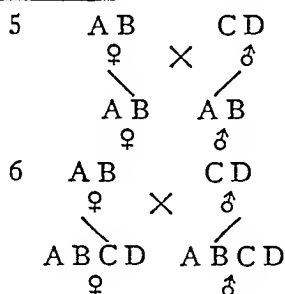
Intracellular invaders among the higher invertebrates are not restricted to insects alone, but have been described as occurring in ticks, mites, leeches and mollusks. Buchner (1922) discussed bacterial "symbionts" in ticks (*Ixodidae*). The species investigated by him did not possess closed organs or mycetomes, but mycetocytes within the malpighian tubules. The plasma of these cells is filled with large numbers of threadlike bacteria often compressed into masses. The micro-organisms appear within young oocytes, in which they congregate in a definite zone. Thus, transmission to future generations is assured.

Reichenow (1921, 1922) found mycetomes harboring "symbionts" in two blood-sucking gamasids, namely, *Liponyssus samarum* (a parasite of the lizard) and *L. musculi* (a parasite of the mouse). The mycetomes of the mites, three in number for each sex, border on the midintestine. Reichenow believed that the cells of the mycetome are derived from the intestinal epithelium and emphasized the close relationship between the micro-organisms and the digestive activities of the host. Reichenow often found two separate species of symbionts within the same species of mite, in other words, that disymbiotic relationships exist. More remarkable than this, however, is the fact, never observed in insects, that in separate individuals of the host species totally different invaders are often present dependent on the localities in which the mites were obtained. However, the descendants of a particular mite always harbor the same micro-organisms as the mother. Four distinct invaders are found. When two occur in one host, they are segregated in different cells and both occur within the three mycetomes to which reference has been made. The micro-organisms appear bacteria-like, often forming long threads, 57 microns long or less, which are coiled into spheres within the mycetocytes. The ova at a certain stage are ejected from the ovary and lie free in the body cavity in close proximity to the mycetomes. At this time, the transfer of the symbionts occurs, long before the eggs are enclosed within their uterine chorionic secretions. By the time the ova reach the uterus, two species of symbionts may be found within the yolk. When the nymph hatches, the intestinal epithelium and mycetomes are already formed. Reichenow did not follow the symbionts into the embryonic mycetomes.

Reichenow's observations on the invasion of the same species of mites in different localities by different symbionts is certainly interesting and may show that particular races of the host species must have remained rather isolated from one another. This, of course, can be

true only if the vertebrate hosts on whom the mites feed remained segregated. It may not be amiss to suggest, however, that perhaps the symbionts observed in different localities may be identical, except for racial or type differences produced by metabolic locality differences within the respective hosts. Indeed, Reichenow himself stated that a certain mite feeds on several distinct species of lizards. An attempt should be made to cultivate and study culturally, biochemically and serologically the various forms encountered. If cultures fail, light on the matter might be obtained by the experimental introduction of the symbionts from one locality into the same species of mites from another by crossing. Thus, a female harboring symbionts *A* and *B* from one place crossed with a male harboring symbionts *C* and *D* from another place would yield progeny, males and females, with symbionts *A* and *B* only, if, as in insects, the transmission is effected through the female to males and females.⁵ The result of such a cross would not signify much. If in mites, however, both sexes transmit symbionts, one would obtain all four of the micro-organisms within the offspring.⁶ If the micro-organisms are really distinct species, the two experimentally introduced forms will probably maintain their identity. If the four symbionts are not distinct but simply environmental forms, the host will soon reduce them to two forms. Of course, it must be determined that the new host does not violently react and destroy the foreign invader, but this supposition seems unreasonable because, in this case, the new and the former hosts are identical species.

Reichenow (1922) also found symbionts in the leech, *Placobdella catenigera*, a parasite of turtles. The esophageal glands of this leech are really mycetomes filled with bacteria-like forms. After the digestion of the blood has commenced, the micro-organisms are also found in the posterior end of the stomach. Thus, Reichenow believed, shows that they have an important digestive function. The author further made the general statement that bacteria are essential to all higher animal life and that in blood-sucking forms, or, in other words, in forms that feed on sterile food, bacterial contamination is provided for by the intracellular symbionts. It might, however, be well to call attention to the fact that Guyénot, Loeb and Northrop, Baumberger, Wollman, I and others have reared many generations of several species



of flies under absolutely sterile conditions. Furthermore, it is known with certainty that some of these insects in the wild state, and the same forms experimentally reared without micro-organisms or their products, do not harbor intracellular symbionts.

Reichenow found all very young leeches infected with symbionts, so that he felt fairly confident that the invaders are transmitted from generation to generation. From his sections, however, he was unable to determine just when and how the transmission occurs.

A PRIMITIVE CASE OF INTRACELLULAR "SYMBIOSIS"

In all the cases of intracellular symbiosis discussed, the mechanisms evolved to assure transmission to succeeding generations are rather complicated. A simple and perhaps recent stage in the evolution of the curious association is exemplified in *Anobium paniceum*, a small beetle commonly occurring in flour, cereals, dried vegetables, etc. Escheich (1900) found certain cells in a section of the midintestine of all individuals of this species filled with yeasts undergoing active multiplication. Transmission to succeeding generations is assured, but the micro-organisms stick to the outside of the eggs, they do not enter them. The female eliminates the yeasts with the feces, and at the time of oviposition the chorion of the eggs becomes contaminated. On hatching, the larvae become infected as they gnaw their way out of the shell. Buchner later found that the yeasts survive the metamorphosis of the beetle by invading the imaginal disks.

HISTOLOGIC TECHNIC

Buchner (1923, 1925), Hertig and Wolbach (1924) and others have emphasized the difficulties encountered during the process of fixing, sectioning and staining material for studies on the intracellular symbionts and their relations to the host. Some of these difficulties are apparently those experienced by all workers requiring insects for histologic or microscopic purposes, and are usually due to the presence of chitin in the epidermal layer and tracheae, which prevents the proper penetration of fixatives and also causes further trouble during the sectioning process. With the exercise of patience and ingenuity, many workers have overcome these obstacles in one way or another. Nevertheless, the symbiont problems present a number of specific hindrances that are not so easily eliminated. Thus, Buchner observed that fixed and stained material is often confusing, and that whenever a heavy infection by symbionts occurs sections are frequently utterly hopeless. Either the micro-organisms do not stain at all, although the host tissues stain perfectly, or they and the tissues absorb the dye to such an extreme that nothing can be observed. If differentiation is then prac-

ticed, or if one decolorizes the symbionts to such an extent that one can actually observe some of the individuals and their structures, the host tissues will often be completely destained and orientation is impossible. This has frequently been my experience, as well as the experience of Buchner, and also of Heitig and Wolbach, who found that the symbionts of the bedbug stain poorly in sections. Investigators have therefore often been compelled to resort to a study of fresh tissues in conjunction with those histologically prepared. Much has been learned by macerating and triturating, in insect blood or in other isotonic fluids, excised ova, mycetomes or tissues containing individual mycetocytes. Often after such manipulations, the symbionts can be properly fixed and stained. Little can be learned in this way, however, concerning the embryologic phases, or the relationships of host and parasite.

If sections are prepared, they should be cut as thin as is practicable for a proper interpretation of the host tissues and their relations, and they may be stained with Heidenhain's or Delafield's iron hematoxylin, some counter dye, such as eosin or orange "G," being used. Fixation of the tissues may be effected with Petrunkevitch's mixture, or with Carnoy's, Flemming's or Bouin's fluid. Before fixation, various openings must be made in the body if the whole insect is used, and before it is embedded in paraffin most of the epidermal chitin should be removed. A method by Dahlgren (1898), combining paraffin and celloidin during the embedding process, proves extremely helpful in handling heavily chitinized material and prevents the tearing of the ribbons.

Specially prepared sections, at times, reveal both intracellular symbionts and mitochondria within the same cells. When the symbionts are rod-shaped, flexed or filamentous in form, as is often the case, the similarity between them and mitochondria may be pronounced. This fact has in the past caused much confusion. Some workers have considered mitochondria to be bacteria, others have identified the symbionts of blattids and ants as mitochondria. More recently, the former view has been generally extended by Portier, Meves and Wallin, who claim that mitochondria are in reality micro-organisms that symbiotically dwell within all animal and plant cells. Portier's views, when they first appeared, in 1918, created so much interest that in 1919 the Biological Society of France appointed a commission to test them. The experiments which were performed at the Pasteur Institute, showed that the so-called mitochondria cultivated by Portier from apparently sterile animal tissues were indeed bacteria that could be traced to contaminations. Wallin (1922) again revived the matter. His results were answered by the counter-experiments of Cowdry (1922), who showed that mitochondria presented totally different micro-chemical and

tinctorial properties from those of bacteria. Nevertheless, Wallin (1928) persisted in his views and published further experiments in their support.

So far as insect tissue is concerned, it can be stated that the intracellular symbionts and mitochondria are separate entities. When tissues are specially prepared and stained with Janus green, mitochondria are found within almost all cells. Under such conditions, the cells do not reveal the class of micro-organisms here discussed. When the tissues are prepared in another special manner, the symbionts are revealed and not the mitochondria. The micro-organisms are ordinarily restricted to particular organs or to isolated cells, whereas the mitochondria are universal. Lastly, cells infected with symbionts are usually packed with the invaders, little else being visible, except the nucleus. Mitochondria, on the other hand, do not completely fill the cytoplasm in this manner.

REACTIONS OF THE HOST TOWARD THE "SYMBIONTS"

The invertebrate host, although often apparently overwhelmed with symbionts, seems not to suffer any serious consequences. In other words, death of certain individuals directly traceable to infection by symbionts has not been recorded. Berlese (1906) estimated the number of fungi present in a single coccid, *Ceroplastes ruscii*, to be between 60,000 and 70,000 cells. It is remarkable that in such forms as coccids and bedbugs, in which the blood distributes and generalizes the infection, no ill to the animals can be observed. These facts signify that the invaders and their activities may be inhibited or controlled to a certain extent, otherwise they would indefinitely multiply and destroy the host.

The mycetomes and mycetocytes show deformation of plasma, but the nucleus usually divides normally. The host is well adapted to its residents as evidenced by special receptor organs and cells, the mycetomes and mycetocytes, which are well tracheated. Complicated arrangements for transmission also exist and definite numbers of symbionts always enter the ova at identical places, usually at the posterior pole.

In spite of these adaptations, certain indications exist that point to a survival of more serious injury and to the former parasitic tendencies of the invaders. Developing mycetocytes often show an abnormal number of chromosomes. In coccids, 100 chromosomes exist in these cells, in contradistinction to twenty within the nuclei of the other somatic cells. Schiadei (1920) also found that the mycetocytes of *Trialeurodes* possess double the number of chromosomes as the other somatic cells. Amitosis within the mycetocytes of *Periplaneta* is rather a common occurrence, and the tissues of *Cimex*

react by producing multinucleated giant cells. The nuclei of all infected cells become more heavily charged with chromatin, and fusions or agglutinations occur, forming large masses. The nucleoli also often multiply abnormally, and complete nuclear degeneration occurs at times. Indeed, in *Aleuodes* and in an African *Cicada*, Buchner at times observed complete dissolution of nuclei and their cells. Similar phenomena often occur in parasitic infections in other animals, and therefore the abnormalities observed in insects are suggestive. The facts mentioned are worth considering before one accepts the popular mutualistic view.

ATTEMPTS TO CULTIVATE THE INTRACELLULAR SYMBIONTS ON ARTIFICIAL MEDIUMS

The cultivation of many of the intracellular symbionts is highly desirable. Each real success would tend to dispel the notion, expressed by Cuénot, Piénant, Henneguy and others, that intracellular symbionts are products of cellular metabolism and not independent micro-organisms. It is, moreover, the only way in which it can be definitely established whether any particular host harbors one or several distinct invaders. In cases in which two or more morphologically distinct forms of fungi exist, the matter may not be so important. However, in the many cases in which invertebrates are found harboring bacteria-like, highly pleomorphic micro-organisms, often of small size, it is certainly important to know whether one is or is not confronted with separate species, or varieties, and whether a single species can be typed or not into separate races. This matter is important practically, for diagnostic purposes, in dealing with some of the pathogenic forms commonly known as "the rickettsiae."

By means of pure cultures, it will further become possible to study the enzymic or biologic activities of the symbionts, which may be correlated in some way with the metabolic activities of their hosts. Such investigations might possibly enlighten us on the question of mutualism.

Some investigators, in fact, have approached the subject from the cultural side, but in most cases the reported successes could not be verified and were invariably traced to contaminations. It is not strange that a group of highly adapted and specialized micro-organisms should present difficulties on artificial mediums. This obstacle can probably be overcome only through the application of special methods and specialized food and temperatures.

Schwartz (1924) believed that every reported success in the cultivation of the symbionts of aphids and scales can be traced to contaminations. Buchner (1925) more or less supported this view. Javelly (1914) and Hertig (1921) also pointed out the pitfalls into which those investigators fell, who described successes in cultivating the bacterioids of the blattids.

Blochmann (1887), Forbes (1892) and Lindner (1895) were among the first to attempt the cultivation of the intracellular symbionts, but were not successful. Successful reports have emanated from Monez (1887), Escherich (1900), Beilese (1905), Conté and Faucheron (1907), Mercier (1906, 1907), Pierantoni (1910), Peklo (1916), Brues and Glaser (1921) and Schwartz (1924). However, on the basis of the criticisms made by Buchner, Javelly, Hertig and especially Schwartz, it is well to assume a sceptical attitude toward all reports of the cultivation of intracellular symbionts. Schwartz's work in 1924, however, because of its careful execution, seems worth recording in some detail. This investigator used seven species of scale insects of the genus *Coccus* (*Lecanum*), two members of the genus *Ceroplastes* and one of the genus *Pulvinaria*. Schwartz introduced the fungus symbionts, taken under sterile precautions from the insects, into moist chambers containing lymph or other special isotonic, well buffered mediums. Of 552 such cultures, only 6, or 1.1 per cent, showed any growth. Direct isolation of the symbionts from the insect on nutrient agar or gelatin was not possible. After the few successful "takes" had been obtained, it was possible to adapt the micro-organisms to other mediums and obtain luxuriant cultures. Single cell isolations were attempted, without success. Apparently, it is necessary to provide at least between ten and twenty cells in order to obtain a growth. In cultures, and within the insects, no spores or resting cells were observed. In insects artificially killed, the symbionts grew to long septated cells, which produced branchlike mycelia and died in from eight to fourteen days. Schwartz, therefore, believed that the invaders cannot survive the death of the host and lead a saprophytic existence. Schwartz studied the enzymic properties of four pure cultures of the fungus, as well as its carbon and nitrogen requirements. Since little is known concerning the metabolism of the host, the results with the symbionts must for the present remain indefinite. However, the author stated that if the host derives any benefit at all, it consists in the breaking down of the end-products of its metabolism by the fungi.

The reports of positive cultures in the literature hardly meet modern bacteriologic and mycologic standards. Schwartz's work is probably an exception, and the results reported by Escherich, Beilese and Brues and Glaser may be sound, but in the light of more recent experience these results require verification. In short, it cannot, to date, definitely be asserted that any micro-organism known as an intracellular symbiont has been cultivated outside the host body.

FURTHER REMARKS

It is clear from the preceding accounts that the phenomenon known as intracellular symbiosis is widespread among invertebrates and prob-

ably even more widely disseminated than indicated at present. It is interesting that this state of affairs, with certain modifications, arose in nature again and again in totally unrelated forms. This is no more nor less mysterious, however, than the frequent and independent appearance of true parasitism.

In 1920, I stated that the conditions now known as intracellular symbiosis had their origin in true parasitism, possibly in disease. The facultative and obligatory mycetocytes, and the closed complexes known as mycetomes, are often regarded as wonderful adaptations or residences furnished by altruistic hosts for the benefit of benevolent organisms of another type. Adaptations these structures are, it is true, but they undoubtedly represent what remains of former forts and other defense works and are not modern sanatoriums. In other words, the structures mentioned are survivals of previous profound pathologic changes or lesions, originally effected by vigorous and highly parasitic micro-organisms. That a balance has as yet not been perfectly established was emphasized with illustrations of abnormal numbers of chromosomes, amitosis, multinucleated giant cells and nuclear and cellular disintegration. As will be shown later, some of the micro-organisms involved in these changes are not showing the inevitable senile traits acquired by prolonged sojourns within benevolent cells, but are demonstrating extraordinary vigor by making excursions into the higher animals, in which they multiply actively, and incidentally create much suffering.

Buchner, Reichenow, Roubaud, Floence and others are not impressed with the hypothesis of parasitism. The phenomena also appear to them too orderly for a senseless commensalism, although the supposed benefits which the host and the invaders derive are admittedly by no means clear. The proximity of the micro-organisms to the alimentary canal in blood-feeding forms is considered evidence that a close physiologic relationship to nutrition exists. As pointed out previously, the micro-organisms probably settled where they did because of the presence there of favorable food, and not because their activities were essential to the well-being of the host.

Just how transmission through the egg became established is not known, but in the primitive case of *Anobium paniceum* we have one possible and suggestive step in the process. At any rate, the hosts reacted by gradually inhibiting the invaders to such an extent that the latter were rendered practically harmless. This defensive ability became heritable, but owing to the fact that an orderly transmission through the egg became established at the same time, the invaders could not be eliminated entirely. For these probable reasons, every individual of the species is infected today.

True symbiosis, or the association of plants, of animals and of animals with plants for reciprocal advantages is of rare occurrence.

in nature As discussed by Hertwig (1912) and by Wheeler (1923), social animals frequently not only gather and hold certain animals in bondage, but even protect and serve them, as in the interesting associations of ants with plant-lice, or even ants of other species Such associations correspond rather to the domestication of animals, or to slavery, as practiced by man The ants care for the plant-lice because of an evolved tropism (trophotaxis, trophobiosis) for the secreted honey dew, and steal the pupae of other ants and rear them, to use them later in their own service This condition of affairs rests, consequently, not on equal rights, since the one animal, the ant, brings about the association, while the other is passively led into it

An instance of most complete equal rights or true symbiosis is furnished by a hermit crab and an actinian, *Eupagurus pubescens* and *Episoanthus americanus* The hermit crab inhabits a snail-shell from the opening of which only his legs and pincers protrude On this shell, an *episoanthus* becomes attached and by budding soon covers it with a colony of polyps The actinian is carried from place to place and shares the food which the crab captures The polyps protect the crab with their nettle cells, while by growth they increase the size of the shell occupied by the hermit, thus saving him from constantly finding new abodes and from periodically exposing his soft abdomen to enemies *Episoanthus* undoubtedly began this mode of life as a parasite, indeed, it is really a parasite still, but since the association proves mutually beneficial it is regarded as a case of symbiosis Through evolutionary adaptations, the association has undoubtedly been modified and improved

Another case of true symbiosis is the interesting example elucidated by Cleveland (1924, 1925) It has long been known that termites harbor several large species of protozoa within their alimentary tracts Cleveland discovered that he could defaunate the termites by incubating the insects, by starving them or by subjecting them to an atmosphere in which the oxygen tension had been raised When such termites were so defaunated, they were no longer able to digest the cellulose in the wood on which they feed Cleveland demonstrated that the protozoa are indispensable to the life of the termites It is safe to conclude that the termite is likewise indispensable to the protozoa, because the symbiotic forms encountered are highly specialized and incapable of a free saprophytic existence

Wheeler, in his studies on the relations of social to other insects, stated that symbiosis is probably never realized in its ideal form, unless we except the intraspecific relationships of such social animals as the termites, wasps, bees, ants and man Symbiosis between separate species is rare in nature, as was shown, and when it does occur is by no means a perfectly evident reciprocity

On the basis of this discussion, it seems best, therefore, to refrain from widely propagating the notion that the intracellular micro-organisms widely disseminated among insects are in mutualistic relations with their hosts. While such relations are within the realm of possibility, little proof for these contentions exists. Strong (1925) pointed out how in the tropics free-living saprophytic spirochetes often become parasitic through a commensal stage. It requires no great effort to imagine the passage of parasites through a commensal stage which at length terminates in symbiosis. However, proof of a state of symbiosis must be presented.

For years, *Hydra viridis* was supposed to live symbiotically with certain intracellular algae. As is now well known, some glycine (0.5 to 1.5 per cent) was added to the culture water, the algae disappeared from the animals and the now colorless hydra lived perfectly well. Also, when certain protozoa and actinians that harbor algae are held in the dark, they become free of the invaders and proceed to live and reproduce normally. It may be possible to attack the problem of the supposed intracellular symbionts in a similar manner. In the case of *Anobium*, the chorion of the eggs can certainly be washed free of adhering yeasts. In other cases, Cleveland's technic or radiation might be tried. In large insects in which large mycetomes occur, excision of the organs might prove just as instructive as the castration practiced so successfully on a variety of insects.

Many other matters pertaining to the intracellular invaders require explanation. In leeches, mites, ticks, lice, bedbugs, tsetse flies, ants and blattids, the micro-organisms morphologically resemble bacteria, in cicadas, coccids, aphids and some other forms, they resemble yeasts and the higher fungi. Until most of these forms are artificially cultivated, little can be known concerning their true taxonomic position and biologic activities. Cultures will also settle the affinities of the forms found in cases of dysymbiosis and trisymbiosis. Here lies an extensive field for entomologists interested in bacteriology and mycology.

What becomes of the micro-organisms when the host dies was answered for certain forms by Schwartz, who found that the invaders die, thus precluding a saprophytic existence for the species living today. This may, however, not be true in all cases.

The definite and orderly wanderings, or rather the passive transportations, of the micro-organisms within the bodies of their hosts is puzzling, especially when one remembers that nearly all the forms investigated are nonmotile. Transportation must be furnished in some way, but how? The invaders enter the egg at a prescribed place and in most cases follow definite routes until they locate within the mycetocytes and mycetomes. Later, when the animal matures, they again follow definite channels until the eggs are reached and no egg

escapes infection. In disymbiotic animals, sometimes both forms enter in a mixed condition. We are almost entirely ignorant of the factors that separate them and permit one to go to certain fat body mycetocytes and the other to form a mycetome. Within the eggs, transportation by the vitellophags is possibly often furnished, and within embryos migrating and shifting cells may constantly provide the necessary energy. After birth, the phagocytes and lymph also probably play a decided rôle. No definite knowledge, however, exists about these matters.

When did the relationships discussed first originate? As previously suggested, an examination of certain fossil arthropods might shed some light on this matter.

I have criticized the symbiotic hypothesis, but am inconsistent and retain the old terminology. This is a conservative and convenient procedure, conservative, because it is not certain that some of the micro-organisms are not symbionts, and I merely caution against the surety with which they have been pronounced such, convenient, because workers everywhere use the words "symbiont" or "symbiote" freely and a change to, for instance, "mild parasite" or "harmless commensal" might produce more confusion. Experiments may finally settle the terminology as well as solve some of the problems involved.

(To be concluded)

Notes and News

University News, Promotions, Resignations, Appointments, Deaths — On December 9 the graduates of the school of medicine of the University of Michigan presented to the university a portrait of Frederick G. Novy, professor of bacteriology and director of the hygienic laboratory, in celebration of his sixty-fifth birthday. Doctor Novy has been a member of the medical faculty of the university for forty-three years.

The Philadelphia Pathological Society has awarded the Gerhart medal to Eugene L. Opie, professor of pathology in the University of Pennsylvania.

William F. Petersen, Chicago, and Karl V. Weller, Ann Arbor, Mich., are president and secretary, respectively, of the American Society of Experimental Pathology, the next meeting of which will be held in Chicago in 1930.

Kenneth N. Lynch, professor of pathology in the medical college of South Carolina, has been elected president of the American Society of Tropical Medicine.

Joshiki Morishita, assistant in bacteriology at Yale University and engaged in the study of dental bacteriology and pathology, has died at the age of 33 years.

At Columbia University, New York, Hans Smetana has been appointed assistant professor of pathology, and Claus W. Jungeblut associate professor of bacteriology.

New Department for Research in the Toledo Hospital — This department, which is built in association with the new hospital, occupies 60,000 cubic feet of space and contains laboratories and rooms for animals. Adequate facilities are provided for local physicians who wish to do experimental work.

Brown Orthopedic Research Fellowships — These fellowships, the income of which is \$2,400 a year, are open to physicians and surgeons throughout the country, regardless of race, creed or color. Two fellowships are awarded each year, not later than December 25. For particulars address the Director, Hospital for Joint Diseases, Madison Avenue and 124th Street, New York.

Permanent Science Fund — This is a new fund for advancing scientific research. As trustee of the Permanent Science Fund, the Boston Safe Deposit and Trust Company will receive in trust gifts and bequests. The income will be paid over to the American Academy of Arts and Sciences for disbursement in the aid of scientific research. Applications for grants-in-aid should be addressed to the committee on the Permanent Science Fund, 28 Newbury Street, Boston.

Blood Grouping — Under the leadership of Dr. T. Madsen, president of the committee of hygiene of the League of Nations, and with the collaboration of leading serologists in a number of different countries, including the United States, the test serums, Anti A (group 3) and Anti B (group 2), are being standardized, no doubt with the purpose of recommending the use of a high-titered serum of definite strength in carrying out the blood groupings previous to transfusion. This plan of using high-titered serums for the groupings has already been followed in a rough way by some institutions. The Cooperative Blood Donors' Bureau, which was established in New York City last year under the auspices of the committee on blood grouping of the National Research Council, is supplying such serums, which are capable of clumping an equal volume of the respective corpuscles on the slide in five seconds. Only a relatively small percentage of persons of the two groups possess such active serum. The use of these standard serums will greatly shorten the time necessary for grouping blood and will lessen the number of mistakes made in this test.

Obituary

HARRY TAYLOR MARSHALL, M D,
1875-1929

Harry Taylor Marshall, Walter Reed professor of pathology and bacteriology in the University of Virginia, died on Nov 8, 1929, in Paris. He was born in Baltimore, May 19, 1875. His father, Charles Marshall, was biographer and chief of staff of General Robert E. Lee. He secured the A B degree from Johns Hopkins University in 1894 and the M D degree four years later. He was intern in the Johns Hopkins Hospital, fellow and later assistant in pathology, and from 1903 to 1906 instructor in medicine and pathology in the Johns Hopkins School of Medicine. During 1903 and 1904 he served also as professor of pathology in the Baltimore Medical College. The year 1901 to 1902 he spent with Paul Ehrlich in Frankfurt-on-Main on a traveling fellowship from the Rockefeller Institute. In the autumn of 1903 and the summer of 1904, he worked in Montana on the loco-weed disease of cattle as special pathologist for the United States Department of Agriculture. The results of these studies are summarized in volume 25 of the *Bulletin of the Johns Hopkins Hospital*. In 1906, he was appointed professor of pathology in the University of the Philippines, and at the same time he served also as pathologist to the Bureau of Science and for one year as secretary and registrar of the College of Medicine, Manila. He returned in 1908 to accept the Walter Reed professorship of pathology and bacteriology in the University of Virginia, where he remained the rest of his life.

He was a member of the Virginia Tuberculosis Commission from 1915 to 1918, and during the last two years he served as director. He was a member of the Virginia State Board of Health from 1916 to 1924. He was president of the American Association of Pathologists and Bacteriologists in 1922, chairman of the section on pathology of the Southern Medical Association in 1928 and secretary in 1929.

Dr. Marshall gave himself unsparingly to every cause that seemed to him to be worthy of his efforts and his death is a great loss.

H. E. JORDAN



HARRY TAYLOR MARSHALL

1875-1929

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE AGING OF HEART MUSCLE ALFRED E COHN, Am J M Sc **177** 619, 1929

Old age is discussed from a biologic point of view and various theories are presented. Certain diseases appear to depend for their explanation on the processes of growth rather than on accidents dependent on the external environment. In the light of these theories, certain cardiac maladies in which pain is a prominent complaint and which occur in advanced years take on a new and different meaning, not only in the comprehension of their pathogenesis, but also in the provision for their relief.

PEARL ZEEK

ASTHMA AND THE VAGAL INNERVATION TO THE BRONCHI HARRY T R MOUNT, Am J M Sc **177** 697, 1929

Stimulation of the vagi in animals often produces changes in the lungs, such as bronchial constriction, bronchorrhea, cellular infiltration and emphysema, similar to those seen in asthma. In the dog, the fibers involved can be sectioned without untoward symptoms. These experiments suggest a procedure that might be considered in certain cases of asthma.

PEARL ZEEK

THE PANCREATIC TRIAD W N BOLDYREFF, Am J M Sc **177** 778, 1929

Complete loss of pancreatic fluid, either through pancreatectomy or fistulae, produces a "pancreatic triad" of (1) rise in the percentage of blood sugar, (2) decrease of the blood coagulability and (3) leukocytosis.

PEARL ZEEK

INCREASE IN BLOOD SUGAR FOLLOWING THE INGESTION OF GLYCEROL JULIUS FERBER and SOPHIE RABINOWITSCH, Am J Med Sc **177** 827, 1929

Glycerol given to a human being on an empty stomach will produce hyperglycemia. The extent of the hyperglycemia is in direct ratio to the disturbance of carbohydrate metabolism of the particular person. In the more progressive cases of diabetes, the glycerol may produce glycosuria, as well as hyperglycemia. These facts warrant the conclusion that in the human body, glycerol is converted into dextrose.

AUTHORS' SUMMARY

SYSTEMIC HISTAMINE-LIKE REACTIONS IN ALLERGY DUE TO COLD BAYARD T HORTON and GEORGE E BROWN, Am J M Sc **178** 191, 1929

Six cases are reported in which local and general symptoms of cold allergy were exhibited. The local effects on the skin were pallor during the period of exposure, and subsequent redness, swelling and increased heat of the hands after removal from the cold. A characteristic systemic reaction appeared, following a latent period of from three to four minutes, which was characteristic of that produced by histamine. There was a fall in blood pressure, a sharp rise in pulse rate, flushing of the face, a tendency to syncope, with transitory recovery in from fifteen to thirty minutes. Complete recovery from the local reaction occurred in from twelve to twenty-four hours. The experimental work which was carried out gave evidence of the chemical nature of these reactions, and strongly suggested the release of a histamine-like substance in the skin following exposure to cold, this substance, when carried in the general circulation, produced a reaction characteristic of histamine. These cases are amenable to treatment. By daily immersion of the hands in cold water, decreasing in temperature, for increasing periods,

excellent results may be obtained. These clinical observations are further confirmation of the work of Lewis and his associates on the presence of histamine or allied substances in the skin of human beings

AUTHORS' SUMMARY

FAMILIAL GLYCOSURIA. REPORT OF A LARGE FAMILY. H. M. BABCOCK, Ann Int Med 2 923, 1929

Eighteen members of one family (representing 58 per cent of the persons studied) were found to have a reducing substance in the urine in the absence of other symptoms or signs of diabetes mellitus. The glycosuria was present in four generations.

WALTER M. SIMPSON

BASAL METABOLISM IN POLYCYTHEMIA VERA. T. L. BLISS, Ann Int Med 2 1155, 1929

Of twenty-three patients with polycythemia vera, 15 (65 per cent) showed an increase of the basal metabolism rate above the normal range of plus 10 per cent. There is no constant relationship between the basal metabolism rate and the increase in blood volume, the cell volume, the erythrocyte count or the concentration of hemoglobin.

WALTER M. SIMPSON

THE INEFFECTIVENESS OF HIGH DOSES OF IRON IN CURING ANEMIA IN THE RAT. J. WADDELL, H. STEENBOCK and E. B. HART, J Biol Chem 83 243, 1929

Iron salts which have been carefully purified from contaminations of copper salt are ineffective for the correction of the anemia induced in young rats by maintenance on a milk diet.

ARTHUR LOCKE

FURTHER PROOF THAT THE ANEMIA PRODUCED ON DIETS OF WHOLE MILK AND IRON IS DUE TO A DEFICIENCY OF COPPER. J. WADDELL, H. STEENBOCK, C. A. ELVEHJEM and E. B. HART, J Biol Chem 83 251, 1929

Young rats which have become anemic after maintenance on a diet of whole milk and iron show an equally rapid return to the normal after the addition to their ration of liver, liver extract, liver ash, the copper-containing fraction of that ash or equivalent preparations of copper sulfate. "This is additional and convincing proof that the deficiency of this basal diet is *inorganic* in nature and that this inorganic deficiency is copper only."

ARTHUR LOCKE

THE EFFECT OF AVITAMINOSIS ON HEMATOPOIETIC FUNCTION. B. SURE, M. C. KIK and D. J. WALKER, J Biol Chem 83 375, 387 and 401, 1929

There is no relation between vitamin A deficiency and pernicious anemia. Deficiency of either vitamin A or vitamin B may be reflected in a slight initial anemia, followed by a later increase in the red cell count, which is occasioned by the associated anhydremia. Vitamin E appears to be without effect on the hematopoietic function.

ARTHUR LOCKE

EFFECT OF HISTAMINE AND OF LOCAL INJURY ON THE BLOOD VESSELS OF THE FROG. R. T. GRANT and T. DUCKETT JONES, Heart 14 339, 1929

Local injury to minute vessels of the frog's tongue causes (a) a local and active dilatation independent of the nervous system and (b) a surrounding secondary dilatation dependent on the integrity of a local nervous mechanism and corresponding to the "flare" of the human reactions. The local reaction is caused not by direct injury to blood vessels but to some chemical substance released from the damaged tissues. In the human being, this substance is probably histamine. However, histamine causes no dilatation of the frog's blood vessels, either when

applied locally or given intravenously The effect in the frog is probably due to a base of the histidine-arginine fraction from skin extracts of the animal

PEARL ZIEK

EFFECT OF ERGOSTEROL ON THE AORTA OF RABBITS R MANCKE, Arch f exper Path u Pharmacol **141** 228, 1929

On addition of irradiated ergosterol to the food of rabbits, marked calcification of the aorta with aneurysmal dilatation resulted regularly

THYROID GLAND IN PREGNANCY AND THE REACTION OF REID-HUNT R BRUEHL, Klin Wchnschr **8** 254, 1929

The resistance of mice against acetonitril poisoning is increased, not only after feeding thyroid substance, but also after giving blood taken from cases of hyperthyroidism An increased thyroid function in pregnancy is generally accepted

The blood from pregnant women was given to mice by mouth and later by subcutaneous injection, and the reaction of Reid-Hunt was determined in the animals No substances which increase the resistance of mice against acetonitril poisoning could be demonstrated in the blood of pregnant women

Therefore, an increased thyroid function in pregnancy is questioned, in spite of the enlarged thyroid gland, the elevated basal metabolism and the high level of iodine in the blood in pregnant women

C A HELLWIG

THE FUNCTIONS OF THE STOMACH IN HEART AND KIDNEY DISEASES J FLIEDERBAUM and N PIANKO, Klin Wchnschr **8** 1076, 1929

Diseases of the heart and kidneys without edema and uremia are not associated with variation of the stomach function When kidney insufficiency is associated with increased blood urea there is often an increased excretion of urea by the stomach With cardiac and renal edema, the acidity and the chloride content of the gastric secretion are diminished and the excretion of neutral red after its injection into muscles is delayed These disturbances do not occur when the edema is caused by local ulcerations The variations in stomach function are independent of the intensity of the lesions of the heart and kidneys They are parallel with the edema of the skin, the dryness of the mouth and with the oliguria These may precede the appearance of the edema, and the results justify the conclusion that extrarenal factors are important in the origin of edema, as stated by Volhard

AUTHORS' SUMMARY

THE RHYTHMIC FUNCTION OF THE LIVER AND ITS SIGNIFICANCE FOR CARBOHYDRATE METABOLISM IN DIABETES AND INSULIN TREATMENT E FORSCREN, Klin Wchnschr **8** 1110, 1929

That food intake is the regulating factor of the liver function and of the internal metabolism has been given too much emphasis Consideration must be given to the fact that the liver has the rhythmic function of alternate assimilation and dissimilation, which to a certain extent is independent of food ingestion This rhythmic function of the liver certainly is important in carbohydrate metabolism, under normal conditions, as well as in diabetes The administration of insulin should be correlated not only with food intake, but especially with internal metabolism

AUTHOR'S SUMMARY

BEHAVIOR OF CHOLESTROL ESTERS IN THE SERUM WITH LIVER DISEASE H WENDT, Klin Wchnschr **8** 1215, 1929

While the bile of man has a cholesterol ester splitting ferment and therefore contains only cholesterol, the bile of dogs has both cholesterol and cholesterol esters, but no ester splitting ferment Even the dog's liver has little ester splitting ferment After ligation of the ductus choledochus in dogs, bile enters the

blood, and there is a parallel increase of cholesterol and cholesterol esters. In man, especially with severe icterus, there is commonly a diminution of the cholesterol esters. This difference in hosts is correlated with the cholesterol ester-splitting ferment of the bile in man.

AUTHOR'S SUMMARY

THE LACTIC ACID VARIATIONS OF THE BLOOD IN MORBUS BASEDOWI IN REST AND DURING WORK. A. BIER, *Klin Wchnschr* 8 1306, 1929

The lactic acid content of the blood of patients with morbus basedowi during rest is regularly increased. It is either above or at the upper normal limits. With slight effort which in health is scarcely work there is such a marked increase of the lactic acid content that it must debilitate and explain the easily produced fatigue. This increase is proportional to coincident variations in oxygen consumption.

AUTHOR'S SUMMARY

RELATION OF HEREDITY AND AGE TO OCCURRENCE OF JUVENILE DIABETES MELLITUS. R. PRIESEL and R. WAGNER, *Klin Wchnschr* 8 1398, 1929

The maximum incidence of juvenile diabetes mellitus in the thirteenth year indicates a close relationship between the number of available islets and growth. There is always a congenital deficiency of islets. The manifestation of latent diabetes is dependent primarily on the number of available islets. Juvenile diabetes often is actually not progressive, but only appears to be so. It is hereditary like deformity. Hereditary relations were established in 27 per cent. The greater incidence (43 per cent of their cases) of heredity in diabetes among Jews is due to inbreeding. Diabetes mellitus is inherited as a recessive, as well as a dominant, character.

AUTHORS' SUMMARY

Pathologic Anatomy

MECONIUM ILEUS WITH CONGENITAL STENOSIS OF THE MAIN PANCREATIC DUCT. BORRIS A. KORNBLITH and SADA O. OTANI, *Am J Path* 5 249, 1929

A case of meconium ileus is presented with the rare anomaly of congenital stenosis of the duct of Wirsung. The absence of pancreatic juice caused inspissation of meconium, with subsequent intestinal obstruction, ileus and perforation.

AUTHORS' SUMMARY

THE PERCENTAGE OF THE DIFFERENT TYPES OF CELLS IN THE MALE ADULT HUMAN HYPOPHYSIS. A. T. RASMUSSEN, *Am J Path* 5 263, 1929

The necessity of a more accurate estimation of the relative number of the different types of cells in the anterior lobe of the hypophysis in man is evident from the great divergence of opinion that exists even among recent writers in regard to what should be considered normal proportions, and from the greater attention that is being paid to pathologic conditions of this organ. The results of making a differential count of the chromophobes, acidophils and basophils in the hypophyses of 100 selected and supposedly normal male adults in cases of sudden and accidental death, in which the tissue in general was fixed within twelve hours after death, are presented. The data are based on a differential count of from 10,000 to 30,000 cells from 100 to 350 microscopic fields taken systematically from three different regions of a complete series of horizontal sections from each hypophysis. The chromophobes represent, on an average, 52 per cent of the total cells. They vary from 34 to 66 per cent. The coefficient of variation is 15. The acidophils average 37 per cent, varying from 23 to 59 per cent, the coefficient of variation being 21. The basophils strictly within the anterior lobe are the least numerous and the most variable. The average is 11 per cent, but they range from less than 5 per cent to more than 27 per cent. The coefficient of variation is 34. Fourteen cases showing a body weight of from 200 to 330 pounds (90.7 to 149.7 Kg.) averaged 3.5 per cent

more chromophobes and 46 per cent less acidophils when compared with eighty-six cases showing a weight of less than 200 pounds. Statistically this difference is not enough to be taken seriously, although the decrease in acidophils is probably real. There is no correlation of importance between body length and percentage of any particular type of cell. Persons over 50 years of age average nearly 4 per cent more chromophobes and correspondingly less acidophils. There is no correlation between age and basophils in the anterior lobe of the hypophysis.

AUTHOR'S SUMMARY

A MALIGNANT MEDIASTINAL TERATOMA WILLIAM F JACOBS, *Am J Path* 5 275, 1929

A case of malignant teratoma is reported. A resume of the literature indicates that these tumors should be classed as teratomas rather than as dermoids. About 10 per cent of these tumors undergo sarcomatous or carcinomatous transformation.

AUTHOR'S SUMMARY

TWO OF THE RARER CONGENITAL ANOMALIES OF THE HEART ISTVAN GÁSPÁR, *Am J Path* 5 285, 1929

A congenital anomaly of the heart is presented, in which an isolated transposition of ventricles occurred. Both large arteries, the aorta and the pulmonary artery, arose from the left ventricle. This is explained by an imperfect rotation of the septum trunci which divided the truncus arteriosus, causing an aortic stenosis. A very small subaortic defect was found. The independent behavior of the ductus arteriosus and its importance in relationship to the dangerous results of the case are also pointed out.

AUTHOR'S SUMMARY

MYELOBLASTIC SARCOMA OF THE CRANIUM EDWIN F HIRSCH, *Am J Path* 5 303, 1929

A large myeloblastic sarcoma of the skull with metastases into the right and left deep cervical lymph nodes and into the right lung is described in this report. The tumor and its metastases contained cells that resembled cellular components of the bone-marrow.

AUTHOR'S SUMMARY

TERATOMA OF THE NECK O SAPHIR, *Am J Path* 5 313, 1929

The literature of teratoma of the neck is reviewed and a new case reported. This is a case of a teratoma of the neck in the region of the thyroid gland in a stillborn colored girl. The main constituent of this tumor was brain tissue but derivatives of the three germinal layers were present. For the first time, groups of cells resembling blood islands are described in this tumor. Even though the location suggests the thyroid gland as the origin, it is more likely that the tumor arose in the area around this gland. The tumor is classified as an embryoid teratoma according to Budde, and as a coetaneous teratoma according to Askanazy.

AUTHOR'S SUMMARY

THE VESSEL CANALS IN NORMAL AND PATHOLOGICAL BONE HENRY L JAFFE, *Am J Path* 5 323, 1929

Volkman originally reported on the formation of numerous new vessel canals in bone in cases of inflammatory osteoporosis, caries and osteitis, and the presence of a few such canals in normal bone. If the term Volkman canal is used exclusively to designate the structure described by him, then his original conception, that the canals result from the canalization of adult bone by newly formed vessels, is correct. As soon as the term is used to designate such canals as Schwalbe described in ground lamellae, or Auhansen in the middle portion of the compacta, or Schaffer and his co-workers in fetal bone and the bone of the

new-born, one is applying the same name to different structures. In normal bone the canals (other than the haversian canals and the canals of the ground lamellae) which have resulted from the deposition of bone around preformed vessels, and thus are surrounded by lamellae, should be termed communicating vessel canals. These include most of the canals which join the haversian canals. This type predominates. The canals which have resulted from the resorption of formed bone by newly formed vessels, exemplified by those which have ragged borders and no lamellae, are the only canals which correspond with those originally described by Volkmann, and may be called Volkmann's canals. In normal lamellar bone there are very few.

AUTHOR'S SUMMARY

ELECTRIC SHOCK H. E. MACMAHON, *Am J Path* 5 333, 1929

The literature dealing with the pathologic changes in the nervous system of electrocuted animals is reviewed. The observations in normal animals, animals with exposed viscera and animals under atropine which were receiving electric shock are described in detail. The value of repeated sublethal shocks in obtaining histologic lesions is stressed. The role of the nervous system in producing changes in other systems is discussed. The gross and microscopic lesions are described in which it is shown that the lesions are confined almost entirely to the nervous system and skeletal muscle. The discussion deals with physical properties of electrical currents, the resistance of the body to currents and the different types of death from electric shock, and emphasis is laid on the importance of prolonged rest in cases of recovery.

AUTHOR'S SUMMARY

MULTIPLE FOCAL SPLENITIS OF GUINEA-PIGS WILLIAM H. FELDMAN, *Am J Path* 5 371, 1929

Twenty-one cases of a spontaneous disease of guinea-pigs which is characterized by a multiple focal type of splenitis, were studied. Morphologically the disease seems to be confined to the spleen, and microscopically the lesions are those of focal necrosis. In an attempt to produce the condition experimentally, thirty-three guinea-pigs were inoculated with emulsions of the lesions from thirteen of the diseased animals. Twenty-five of the experimental animals died, the most frequent lesions were those of purulent or fibrinous peritonitis. From many of the inoculated animals which died, a gram-positive streptococcus was obtained. The spleens of a few of the experimental animals possessed microscopic lesions similar to those observed spontaneously. The impossibility of ruling out spontaneous cases of the disease in the experimental animals makes it unwise to assume that the specific lesions have been produced experimentally. For the same reason there does not seem to be any correlation between the condition known as purulent adenitis and the splenic disease described.

AUTHOR'S SUMMARY

INVOLVEMENT OF MEDIUM-SIZED ARTERIES ASSOCIATED WITH SYPHILITIC AORTITIS OTTO SAPHIR, *Am J Path* 5 397, 1929

Among fifty cases of syphilitic aortitis, the innominate artery showed syphilitic changes in thirty-three, the carotid in twenty-nine, the superior mesenteric in ten, the inferior mesenteric in three, the common iliac in ten, and the femoral artery in seven cases. The subclavian artery was examined in twenty-nine cases, fifteen of which showed syphilitic lesions. The syphilitic lesions were characterized by endarteritis of the vasa vasorum, and perivascular infiltration of lymphocytes in the adventitia. The media of the elastic type of arteries showed an interruption of the continuity of the elastic fibers and fibrotic areas, combined with circumscribed lymphocytic infiltrations. The media of the muscular type of arteries only rarely showed changes. In the intima, circumscribed button-like areas of fibrosis, without degenerative changes, were found frequently. These were not specific but were chronic inflammatory and might be associated with any type of pathologic lesion in the adventitia.

AUTHOR'S SUMMARY

ACCESSORY PANCREAS ROBERT A MOORE, *Am J Path* 5 407, 1929

A case of accessory pancreas in the wall of the ileum in a child, aged 1 year, is reported. The mode of origin of these congenital anomalies is either by adhesions of the main pancreatic anlage or from anomalous anlage. Accessory pancreases are in rare instances the underlying cause of diverticula and intussusception and the site of origin of carcinoma.

AUTHOR'S SUMMARY

LYMPHANGIECTATIC CYST OF THE LEFT LABIUM MINUS C J LUNSFORD and G C SCHAUFFLER, *Arch Dermat & Syph* 19 945, 1929

A patient with a lymphatic cyst involving the labia minora is added to the five previously reported instances. This account is of interest in that the cyst was limited to the labia minora.

FRANK M COCHEMS

GROSS AND MICROSCOPIC CHANGES IN THE SKIN PRODUCED BY X-RAYS AND BY LIPOID SOLVENTS L H JORSTAD and C W LANE, *Arch Dermat & Syph* 19 954, 1929

Active precancerous lesions histologically were produced in the skin of the white rat by repeated paintings with a diluted tar preparation. The same type of lesion was produced by a single exposure of unfiltered x-rays or by combining the two procedures. In observing the histologic changes produced by these procedures at different intervals throughout the period of experiment, further evidence was gained that coal tar, allied substances such as mazola oil, paraffin oil and foot oil, and roentgen rays act similarly in inducing a malignant condition. They act as lipid solvents.

AUTHORS' SUMMARY

CHRONIC DERMATOSIS WITH DEGENERATION OF THE COLLAGEN F R HARPER, *Arch Dermat & Syph* 20 201, 1929

A case is reported of a chronic, noninflammatory, widespread, symptomless disease of the skin. In the sections of tissue obtained by biopsy there was swelling and degeneration of the collagen bundles of the subpapillary layer of the corium, with an associated decrease in the size and number of the elastic fibers and an increase in the nuclear elements. The author concludes that the disease is probably a combined degeneration and proliferation involving the subpapillary layer of the corium.

AUTHOR'S SUMMARY

GENERALIZED LYMPHOGRANULOMATOSIS OF THE SKIN J W JONES and H S ALDEN, *Arch Dermat & Syph* 20 212, 1929

An instance of generalized lymphogranulomatosis in a negro boy is reported. The noteworthy features were a generalized intense pruritic eruption, a hyperplasia of the lymph nodes and an ultimate loss of hair. These symptoms give the disease a certain clinical similarity to pityriasis rubra (Hebra). In the histologic preparations of a lymph node from the right inguinal region there were no giant cells.

FRANK M COCHEMS

NEPHROSIS (A CRITIQUE) HENRY A CHRISTIAN, *J A M A* 93 23, 1929

The following conception is advanced of nephrosis as a clinical condition. With a prolonged protein deficit in the blood there will appear edema, lowered blood protein with relative increase of globulin, hypercholesteremia and lowered basal metabolism. The most common cause of deficit in blood protein is albuminuria due to a renal lesion. Often this renal lesion is in the glomeruli, but in patients dying of infection rather early, the glomeruli may be but little altered or not at all, while there are extensive changes of a degenerative nature in the tubules. There

seems "to be no justification for regarding nephrosis as other than a variety of kidney disease, a form of chronic nephritis (Bright's disease)" Clinically nephrosis does not mean that a deposit and single form of lesion is present in the kidney, as there may be degeneration of tubules with normal glomeruli, amyloidosis, or glomerular lesions, furthermore all these changes may occur in patients without any syndrome of nephrosis Nephrosis as a clinical term has no advantage over such terms as subacute or chronic nephritis with edema The use by pathologists of the term nephrosis for degenerative renal lesions may not be objectionable, but clinicians will still be unable to apply a pathologic (anatomic) classification of nephritis accurately in clinical work

ASCARIS LUMBRICOIDES IN CAVITY OF HEART CARL BOETTIGER and JACOB WERNE, J A M A **93** 32, 1929

Two worms were found in the cavity of the right ventricle in a woman, aged 65

ISLET CELL TUMOR OF THE PANCREAS GOLDWIN HOWLAND and others, J A M A **93** 674, 1929

In a case of dysinsulinism of six years' duration, attacks of coma and convulsions increasing in their frequency but warded off by the administration of food were found to be caused by low blood sugar levels A study of the case revealed the erratic response to carbohydrate administration unless suitably administered, and led to the diagnosis of the cause as an islet cell tumor of the pancreas At operation a tumor of the pancreas was found and removed, and a fruitless search for metastases was made The patient recovered and has since been entirely free from the attacks This constitutes the first successful treatment in such a case reported in the literature The tumor was found to be a slow growing carcinoma of the islets of Langerhans, and insulin was recovered from the tumor mass

AUTHORS' SUMMARY

MEASUREMENTS OF THE PELVIS IN HINDU FEMALES N PAN, J Anat **63** 263, 1929

Measurements were taken from the pelvis of sixty-four adult Hindu women The author found that the pelvis of women of this race is 1 cm less in all diameters than that of British or American women The fact that the body of the fetus is comparatively smaller in size prevents obstetric difficulties

A J KOBAK

THE ETIOLOGY OF ACCIDENTAL HEMORRHAGE AND PLACENTAL INFARCTION F J BROWNE and GLADYS DODDS, J Obst & Gynaec Brit Emp **35** 661, 1928

Browne and Dodds reproduced accidental hemorrhage (premature separation of a normally implanted placenta) experimentally in rabbits by first inducing a chronic nephritis in the nonpregnant animal, and caused an exacerbation of the renal lesion after twenty days of pregnancy (corresponding to six months pregnancy in the human being) Sodium oxalate 1 per cent was given at frequent intervals intravenously for three months, after twenty days of pregnancy this was given once more, followed by an injection of an emulsion of *Bacillus pyocyaneus* This was repeated on several rabbits and the results were constant The hemorrhage was retroplacental, intramuscular and at times visible as a bleeding through the vagina The authors offer a newer concept as to the pathogenesis of the associated infarction in the placenta They express their belief that the same process which evokes the toxemia of pregnancy causes the infarction, namely, a circulating endothelial toxin The latter destroys the syncytial living of the villus, permitting a clot to form around it and cut off its source of nutrition This endothelial poison acts likewise on the endothelium of the decidual

capillaries and on that of the vessels in the fibromuscular wall of the uterus and its adnexa. Changes were similarly noted in distant organs, such as the brain, liver and spleen. These experiments were well controlled, and examinations of the urine and blood chemistry were used as checks. Subsequent pregnancies in animals that survived these experiments were associated with spontaneous premature detachment of normally implanted placentae. From their experimental data the authors conclude that chronic nephritis is the essential underlying factor, when it is present, the kidneys cannot normally eliminate the circulating toxins (metabolic or bacterial) but allow them to accumulate and concentrate, and cause capillary endothelium destruction with thromboses and hemorrhages.

A J KOBAK

A CASE OF ADENOMYOLIPOMA OF THE FALLOPIAN TUBE WILFRED SHAW,
J Obst & Gynaec Brit Emp 35 725, 1928

Shaw describes a rare tumor occurring in a nullipara, aged 40, whose chief complaint was irregular hemorrhage. Laparotomy disclosed that there was a left tubo-ovarian cyst, that the right tube and ovary were covered with adhesions, and that the uterus contained fibroids. The right cornu appeared to contain a small lobulated fibroid, which when incised allowed some tarry fluid to escape. The tumor arose from the anterior surface of the isthmal portion of the fallopian tube. Histologically, the glandular tissue in serial sections appeared to be connected with the mucosa but was entirely separated from other glandular spaces that were seen deeper in the muscular planes. These gland spaces were lined partly by cuboidal cells, and no peripheral stroma was present. As there was no connection with the serosal and mucosal surfaces of the uterus, Shaw believes that these deep gland spaces arose by a metaplasia of the endothelial lining of the lymphatic spaces. There were also some muscle and gland spaces among the fat cells of the lipoma. The author does not believe there is any reason for associating the adenomyoma with the chronic inflammatory condition of the tube.

A J KOBAK

INSERTION OF PAPILLARY MUSCLES DIRECTLY INTO THE FRONT MITRAL
LEAFLET H WILLER, Centralbl f allg Path u path Anat 45 209, 1929

Willer describes two hearts in which there was a direct attachment of portions of the left anterior papillary muscle to the front mitral leaflet. The first he observed in a man, aged 63, who was dying of hemorrhage following rupture of the spleen, the second in a woman, aged 26, who was dying of peritonitis. The site of attachment was 65 mm long and 4 mm wide in the first case, and 10 mm long and 4 mm wide in the second. Short chordae tendineae were stretched from the edges of these muscle bands to the mitral leaflets. In both cases there were separate portions of the muscle, some inserting directly and some connecting by chordae. Presumably these muscles are congenital anomalies which may be accentuated by hypertrophy in such a disease as mitral insufficiency.

GEORGE RUKSTINAT

PROGRESSIVE THROMBOPHLEBITIS M LIPSCHITZ, Deutsche med Wchnschr
55 744, 1929

A man, aged 49, with no essential previous history suffered a contusion of the right leg. The resultant swelling of the leg increased and the veins beneath the skin became firm, tender cords. Four months later the left lower leg became swollen and discolored, and the subcutaneous veins also firm and tender. Finally there was thrombosis of the veins of the lower anterior abdominal wall and of the right internal jugular vein. This was followed by ocular paralysis and a left hemiplegia.

Postmortem examination demonstrated thrombosis of the small veins of both legs, of the anterior abdominal wall and of the prostatic plexus. There were mural thrombi of both common iliac veins and inferior vena cava to the level of the renal veins. The lumen of the right saphenous and femoral veins contained canalized thrombi. An organizing thrombus of the right internal jugular vein extended into the dural sinuses and caused hemorrhagic infarcts of the brain. There was a marked senile arteriosclerosis of the aorta with occlusion of the left coronary artery and an aneurysm of the heart. The spleen was enlarged. The leukocytes of the blood were unchanged and the Wassermann reaction of the blood was negative. Blood cultures were also negative.

PAUL J. BRESLICH

UNUSUAL AMYLOID DEPOSITS O. LUBARSCH, *Virchows Arch f path Anat* **271** 867, 1929

In very rare instances, general amyloidosis attacks the organs that generally remain free, and leaves intact or nearly intact the large parenchymatous organs that are usually involved. Lubarsch describes three such cases in detail. In one of them the amyloidosis of the muscle system and the skin had led to a clinical diagnosis of scleroderma and myotony, while the involvement of the tongue gave a picture of carcinoma. The walls of the heart had become so stiff from the amyloid deposits that the heart retained its form after being opened. In the skin the amyloid formed circumscribed nodules. In other respects, too, this condition was intermediate between generalized amyloidosis and localized amyloid deposits. The blood vessels appeared gaping at autopsy due to the stiffness of their walls. The media was mostly affected. The nervous system was practically free. In a second case the involvement of the lymph nodes, together with gastric ulcers, had resulted in a picture of inoperable cancer of the stomach. The third patient showed purpura and diseased gums in spite of good nourishment.

The color reactions were partly anomalous. In the first case no underlying disease could be found. The inflammatory processes (pyelitis urethritis) that could be traced in the two other ones seem unimportant in comparison with the enormous amyloidosis. But, as animal experiments indicate, amyloidosis may become progressive even after cessation of the causative disease.

ALFRED PLAUT

THE PHYSIOLOGY AND HISTOLOGY OF THE MUMMIFIED RABBIT'S EAR B. D. MOROSOW, *Virchows Arch f path Anat* **272** 1, 1929

Organs dried in the exsiccator, even for months, and then softened in water may retain some of their functions. This has been shown in the ear of the rabbit, the fingers of the human being, the intestine of the rabbit and the guinea-pig and the heart of the frog.

Morosow worked on forty dried rabbit's ears. The drying was done in different ways: in the exsiccator, in thin air, at room temperature and in hot air. It was continued until the weight became constant (in from fifteen to 119 days). The loss of weight was from 54 to 73 per cent, the dried ear looked like parchment, but not all the water had left the tissue. The blood vessels of these dried ears reacted to epinephrine (from 0.25 to 1.0 cc), nicotine 1:200, cocaine 1:200, and barium chloride 1:200. No reaction could be obtained with caffeine, caffeine sodium benzoate, chloral hydrate or the faradic current. These dried tissues can be stained as well as normal tissues can.

ALFRED PLAUT

MARKINGS OF THE CUT SURFACE OF LIVER L. LOEFFLER, *Virchows Arch f path Anat* **272** 17, 1929

Acinar markings of the cut surface are pathologic. The really normal liver—which is seldom seen at autopsy—has a nearly homogeneous cut surface. Overgrowth of the interlobular connective tissue leads to a tortuous course of the interlobular veins. These are cut frequently and more or less longitudinally,

hence the red bands of the nutmeg liver. Large livers with small acini are found in hypertension when death has taken place without long illness. Such livers have much parenchyma, little connective tissue but much muscle tissue in the vessel walls. Lobar structure is found in heart disease, mitral stenosis, and cirrhosis—Laennec's as well as the syphilitic type. Overgrowth of connective tissue may take place along the different blood vessels of the liver, and anastomoses may be established in different ways, this leads to different aspects of the cut surfaces. All the manifold pictures are caused by the reactions of the vascular apparatus of the liver. Direct damage to the liver cells plays no rôle.

ALFRED PLAUT

THE INTERVERTEBRAL DISKS. E. BRACK, *Virchows Arch f path Anat* **272** 61, 1929

One fifth to one sixth of the length of the spine belongs to the disks. Too little is known about their normal structure. They are nourished by osmotic exchange mainly, but there are blood vessels at the periphery. The upper and the lower layers consist of cartilage, these layers are thicker in children, and very thick in rickets. There is much variation in the normal shape of the disks. Traumatic tearing occurs even without bone lesion. In some instances of bone atrophy the disks dig a funnel into the middle of the vertebrae. Circumscribed hypertrophy is frequent in the form of Schmorl's "Knorpelknötchen" (cartilaginous nodules). They usually have the shape of a button. They seem single, occasionally double, to the naked eye, on microscopic examination they often are multiple. They are more frequent in men than in women, the thoracic spine harbors them most frequently. Small foci of nucleus pulposus tissue situated in the annulus fibrosus may have something to do with their origin. Their cells store fat, while the normal cells of the nucleus do not. Small margins of bone marrow may become necrotic when touched by a cartilaginous nodule. The edge of the nodule slowly calcifies.

In twelve cases of most severe traumatism, hemorrhage was not found in the disks. In old people, however, brownish discoloration is found occasionally. Atrophy occurs in kyphoscoliosis and in old age. The disks become narrow, and the annulus may become cartilaginous, notably in arthritis deformans. The disks offer a new but difficult field for study. The present study is based on 100 spines.

ALFRED PLAUT

THE PATHOLOGIC ANATOMY OF LYMPHOGRANULOMATOSIS. M. BRANDT, *Virchows Arch f path Anat* **272** 401, 1929

Sixty-five cases were observed in Riga (Latvia) from 1922 to 1928. Mesenteric and retroperitoneal lymph nodes were often affected. The classic textbook picture with main localization on the neck was rare. The spleen was nearly always affected. The eosinophil cells in the tissue are not important for diagnosis. Varying forms of giant cells were found besides the Sternberg cells, some of them resembled the Langhans cell and were phagocytic. The lymphogranulomatous tissue changes indicate a severe damage to the reticulo-endothelium. The causes of such damage are not uniform. Lymphogranulomatosis is no disease in itself.

ALFRED PLAUT

Pathologic Chemistry and Physics

THE EXCRETION OF LEAD IN URINE. H. MILLET, *J Biol Chem* **83** 265, 1929

Lead is a normal constituent of the urine. The daily excretion of the metal by persons who have received injections of colloidal lead phosphate does not appear to exceed that observed in persons not so treated.

ARTHUR LOCKE

BIOCHEMICAL FINDINGS IN A RARE CASE OF ACUTE YELLOW ATROPHY OF THE LIVER, WITH PARTICULAR REFERENCE TO THE ORIGIN OF UREA IN THE BODY I M RABINOWITCH, *J Biol Chem* **83** 333, 1929

A case of idiopathic, acute yellow atrophy of the liver is described. The patient had, functionally, the status of a person from whom the liver and kidneys had been completely removed. No urea was present in the blood and extremely little in the urine, suggesting that the substance may be formed only through the agency of intact liver tissue.

ARTHUR LOCKE

THE HYDROGEN-ION CONCENTRATION OF SWEAT A MARCHIONINI, *Klin Wchnschr* **8** 924, 1929

The p_H of sweat secretion obtained by thermal (light) stimulation and injection of pilocarpine, collected separately from the apocrine and the eccrine glands, differs considerably. The p_H of sweat from the eccrine glands varied between 4.0 and 5.5, that from the apocrine glands between 6.0 and 6.9 with thermal stimulation. With pilocarpine stimulation, the corresponding p_H values were from 5.1 to 7.3 and from 7.2 to 8.6, again showing distinct differences.

EDWIN F HIRSCH

EXPERIMENTAL ALKALOSIS AND THE GASEOUS EXCHANGE IN MAN O WUTH, *Klin Wchnschr* **8** 969, 1929

Fifty grams NaHCO_3 given by mouth to an obese but robust young man (17 years old) cause a marked alkalosis and an increase of the basal metabolism from -3 to +14.

AUTHOR'S SUMMARY

Microbiology and Parasitology

FULMINATING MENINGOCOCCUS SEPTICEMIA WITHOUT MENINGITIS RICHARD MIDDLETON and WILLIAM DUANE, *Am J M Sc* **177** 648, 1929

A case is presented in which a fulminating infection with meningococcus caused death within a few hours, the only clinical and anatomic observations being those of an intense septicemia.

PEARL ZEEK

INFECTION AS A CAUSE OF JUVENILE CIRRHOSIS V H MOON, *Am J M Sc* **177** 681, 1929

Juvenile cirrhosis is a combined disease of liver and spleen. Streptococci were found in these organs in two cases of atrophic cirrhosis in children. The streptococci from one case showed a definite tendency to infect the liver in animals, regardless of the route or site of inoculation.

PEARL ZEEK

RETROPHARYNGEAL ABSCESS IN INFANTS AND CHILDREN HARRY M GREENWALD and CHARLES A MESSELOFF, *Am J M Sc* **177** 767, 1929

The importance of this condition is emphasized in the analysis of fifty-five cases among which the death rate was 73 per cent. Retropharyngeal abscess should be suspected in every case presenting an enlarged cervical gland and the diagnosis determined by digital examination of the pharynx.

PEARL ZEEK

GONOCOCCAL AND PNEUMOCOCCAL VEGETATIVE ENDOCARDITIS OF THE PULMONARY VALVE JAMES I JOHNSTON and JOHN M JOHNSTON, *Am J M Sc* **177** 843, 1929

Two cases of acute lesions of the pulmonary valve are described in which the etiologic agents were presumptively found.

PEARL ZEEK

THE BLOOD SEDIMENTATION TEST IN EXPERIMENTAL POLIOMYELITIS J R KAGAN, Am J M Sc **178** 67, 1929

The sedimentation time for normal healthy monkeys was determined and found to be nineteen hours and thirty-two minutes. The sedimentation time for monkeys with poliomyelitis is considerably shorter, giving an average of two hours and thirty-nine minutes, and showing a marked difference from the sedimentation time for normal monkeys. The sedimentation time for monkeys with tuberculosis, general debility of undetermined nature and superficial infection is still shorter, namely, one hour and twenty minutes.

AUTHOR'S SUMMARY

STRAIN VARIATIONS IN *C. BIFERMENTANS* E T DRAKE and W S STURGES, J Bact **17** 387, 1929

With the assumption that *Clostridium bifermentans* and *C. centrosporigenes* constituted a somewhat unified group, a study was made of all available strains (twenty-one) belonging to this group. Since no consistent differences were found between the strains labeled *C. bifermentans* and those labeled *C. centrosporigenes*, the use of the latter name would seem unjustifiable. The variations observed suggest another and a more logical grouping, but the nature of the variations and the existence of intermediate strains necessitate all of the strains being considered as a single species.

AUTHORS' SUMMARY

THE INFLUENCE OF IRON ON THE PIGMENTATION OF ACID-FAST BACTERIA GUILFORD B REED and CHRISTINE E RICE, J Bact **17** 407, 1929

Data have been presented which indicate that the yellow, brown or red pigmentation of acid-fast bacteria is related to the presence of iron in the culture mediums. Lack of stabilizing substances or high p_H which permits precipitation of the iron prevents pigment formation. Nonacid-fast bacteria are not so affected by the iron content of culture mediums.

AUTHORS' SUMMARY

CLASSIFICATION OF THE STREPTOCOCCI OF HUMAN FECES HENRY WELCH, J Bact **17** 413, 1929

The streptococci of the feces are apparently constant in their fermentative ability. Differentiations should be made only in mediums which are most favorable for the growth of the organism. The results indicate that there are six strains common to stools of human beings. Those fermenting all sugars used, dextrose, lactose, sucrose, salicin, maltose, mannitol, galactose, all but sucrose, all but sucrose and mannitol, all but mannitol, all but mannitol and salicin, all but actose. Serologically, strains *a*, *c* and *d* resemble each other and give slight hemolysis. Strains *b*, *e* and *f* give no hemolysis, and of these *b* and *f* resemble each other serologically, while *c* is distinctly different. There is little in the morphology of the streptococci of the feces of human beings that assists in their differentiation.

AUTHOR'S SUMMARY

THE GERMICIDAL ACTION OF HALOGEN DERIVATIVES OF PHENOL AND RESORCINOL AND ITS IMPAIRMENT BY ORGANIC MATTER EMIL KLARMANN, VLADIMIR A SHTERNOV and JOHN VON WOWER, J Bact **17** 423, 1929

The results of experiments on the disinfectant action of phenol, resorcinol and their halogen derivatives, against *B. typhosus* and *Staphylococcus pyogenes-aureus*, tend to indicate that there is a distinct relationship between the constitution of these derivatives and the impairment of their disinfectant action by organic matter. It is shown that even the exceedingly small quantity of organic matter present in the original culture suffices to produce considerable impairment of the germicidal efficacy of certain compounds. A working hypothesis of disinfectant action is outlined, depending on the assumption of formation of so-called molecular (additive)

compounds of the disinfectant agent with certain free reactive groups in the organic matter, or the protoplasm, respectively, which is to form the basis for further work on the problem

AUTHORS' SUMMARY

THE INFLUENCE OF GASEOUS ENVIRONMENT ON GROWTH AND TOXIN PRODUCTION OF *C. DIPHTHERIAE* WAYNE N. PLASTRIDGE and LEO F. RETTGER, J. Bact. 18 1, 1929

The intracutaneous test, as employed in this investigation, was found to be a reliable and economical means of determining the approximate toxicity of *C. diphtheriae* culture filtrates. Aeration of broth cultures of *C. diphtheriae* with atmospheres containing from 3 to 10 per cent carbon dioxide and from 5 to 50 per cent oxygen resulted in increased growth and toxin production. Aeration of broth cultures with ordinary air or carbon dioxide-free atmospheres containing from 10 to 50 per cent oxygen resulted in marked irregularity in growth and in the toxin content of *C. diphtheriae* cultures. The data obtained show that the higher the oxygen content of the atmospheres passed over the cultures the greater is the irregularity in toxin content of the cultures at the time of harvesting. The rate of destruction of the toxin once it was formed was found to be inversely proportional to the oxygen tension within the culture flask. The optimum oxygen and carbon dioxide tensions for growth and toxin accumulation were found to be supplied by an atmosphere containing from 15 to 20 per cent oxygen and from 5 to 10 per cent carbon dioxide. In the presence of such an atmosphere uniform maximum toxin production occurred in a given medium, and no decrease in toxicity took place on prolonged incubation. The reaction of cultures of *C. diphtheriae* which were grown in meat-infusion broth prepared with Difco-Proteose Peptone was maintained at about p_H 8, 7.8 and 7.5 by aeration with atmospheres containing 5, 10 and 20 per cent carbon dioxide, respectively. The ammonia content of all cultures showed a sharp increase during the period of maximum growth. In the case of the cultures grown under ordinary atmospheric conditions, or aerated with carbon dioxide-free atmosphere, this increase was followed by a gradual decline, as compared to a continuous increase throughout the entire twenty-day incubation period in cultures grown under an increased carbon dioxide tension. The amino-nitrogen increase in cultures grown in broth prepared with Difco-Bacto Peptone, was much less marked than in cultures grown in broth prepared with Difco-Bacto Peptone, presumably due to a dearth of protein derivatives in Difco-Bacto Peptone which are capable of being broken down into amino-acids by the peptolytic enzymes of *C. diphtheriae*. The proteose fractions of certain commercial peptones were found to be necessary for toxin formation for other reasons than their buffering action on decreasing hydrogen ion concentration of the culture medium. Increased carbon dioxide tension was found to prevent the usual rapid destruction of the bacterial cells after the period of maximum growth. The general conclusion may be drawn from the data presented that carbon dioxide plays an important role in the growth and toxin production of *C. diphtheriae*, mainly by acting as either a catalyst or food in stimulating growth and toxin formation, controlling the reaction of the culture medium during growth and preventing the destruction of the toxin once it is formed, by a mechanism which is as yet little or not at all understood.

AUTHORS' SUMMARY

SODIUM CHLORIDE MEDIA FOR THE SEPARATION OF CERTAIN GRAM-POSITIVE COCCI FROM GRAM-NEGATIVE BACILLI JUSTINA H. HILL and EDWIN C. WHITE, J. Bact. 18 43, 1929

It has been found that p_H 6 sodium chloride agars, with salt concentrations from 2 through 20 per cent, exert marked inhibitory action on the growth of bacilli of the typhoid, paratyphoid, dysentery, and colon groups, on species of *Proteus*, *Pseudomonas*, on diphtheroids and on *Bacillus anthracis*. The gram-positive cocci studied tolerate high salt concentrations, all being positive on transfer from 20 per cent sodium chloride agar. In p_H 6 broths, with salt concentrations

from 2 through 25 per cent, the same differential bacteriostasis may be observed, although to a lesser degree than on agar. It has been found that when mixtures of cocci and bacilli in different proportions are cultured on appropriate salt agars, the cocci invariably outgrow the bacilli and may sometimes be recovered in pure culture. The use of 6, 8, 10 and 15 per cent salt agars greatly facilitates the isolation of gram-positive cocci from specimens from mixed infections. The use of such salt agars is therefore suggested for the inhibition of gram-negative bacilli and for the isolation of gram-positive cocci.

AUTHORS' SUMMARY

A CONTINUOUS METHOD OF CULTURING BACTERIA FOR CHEMICAL STUDY.
HARVEY V MOYER, J Bact **18** 59, 1929

A continuous process for culturing bacteria in the laboratory for chemical study has been described. The construction and operation of the apparatus have been discussed. The mass production of *Bacterium aerogenes* has been described.

AUTHOR'S SUMMARY

AN OUTBREAK OF BOTULISM DUE TO HOME-CANNED STRING BEANS. WILLIAM E CARY, STEWART A KOSER and VAN S LAUGHLIN, J Prev Med **3** 317, 1929

An outbreak of botulism at Westfield, N Y, resulting in ten cases with five deaths, was evidently due to home-canned yellow string beans. *Clostridium botulinum*, type B, was isolated from the empty jar which had contained the beans. Another product from the same household, home-canned egg plant, was found to be lightly seeded with *Clostridium botulinum*, type B, though the food itself was nontoxic.

AUTHORS' SUMMARY

THE IDENTITY OF HUMAN LEPROSY AND RAT LEPROSY. ERNEST L WALKER and MARION A SWEENEY, J Prev Med **3** 325, 1929

The morphologic and tinctorial transmutations of the organism of rat leprosy are identical with those of the human strains. The authors are convinced that leprosy in the rat and in the human being has the same etiology and endemology, i e, is caused by an actinomyces infection from the soil. The discovery of this identity is of especial importance because it provides an experimental animal for the study of the disease.

FACTORS INVOLVED IN AN EFFECTIVE TYPHOID CARRIER SURVEY. LEON C HAVENS and CATHERINE RIDGWAY, J Prev Med **3** 335, 1929

A typhoid carrier survey of 225 food handlers in a small Southern city revealed seven carriers (three typhoid and four paratyphoid B). The importance of well organized and carefully planned field work is emphasized as an essential part of a carrier study of any extent. Carrier surveys, particularly of food occupations, yield results, in the Southern States at least, which justify their inclusion among typhoid control measures.

AUTHORS' SUMMARY

SEASONAL VARIATION IN THE SUSCEPTIBILITY OF MICE TO DYSENTERY (SHIGA) TOXIN. ADELAIDE V BLAKE and C C OKELL, Brit J Exper Path **10** 175, 1929

In titrations of dysentery (Shiga) toxin and antitoxin, not only are variations in individual susceptibility to the toxin met with, but also variation effects in groups of mice used at intervals. The variability appears to be seasonal, the mean susceptibility of the mice to the toxin being greater in winter than in the summer months.

The possibility of variations of this type must be considered in titrations of any biologic reagent where the degree of accuracy demanded approaches nearly to the extreme limits permitted by the method of test.

AUTHORS' SUMMARY

THE NATURE OF TUBERCULOUS CASEATION W PAGEL, Klin Wchnschr
8 1352, 1929

In an experiment in which human tuberculous tissues were transplanted into skin pockets of normal and tuberculous guinea-pigs, two varieties of tuberculous softening could be distinguished (1) circumscribed softening in nonallergic animals in close relation with local bacterial proliferation, and (2) extensive leukocyte digestion of the transplanted tissues in allergic animals

AUTHOR'S SUMMARY (in part)

ON LYMPHOGRANULOMATOSIS AND OTHER PECULIAR GENERALIZED GRANULOMAS OF LYMPH NODES K TERPLAN and MARIA MITTELBACH, Virchows Arch f path Anat 271 759, 1929

The authors report observations on twenty-nine cases of lymphogranulomatosis in which complete examinations were made. The total number that came to autopsy in four years was thirty-five. The authors do not believe that lymphogranulomatosis has anything to do with tuberculosis. The histologic pictures of tuberculosis and lymphogranulomatosis when coexistent could be differentiated easily from each other. Animal inoculations were positive in three cases only, in one there was active tuberculosis, and there was an old tuberculous condition in the two other cases. Lymphogranulomatosis is a chronic, specific, infectious disease. The combination with tuberculosis was found in one sixth of the cases. An attempt was made to correlate the main seat of the disease with the localization of the first clinical symptoms, but a definite relation was apparent in the intestinal cases only. It is astonishing that of twenty-nine cases seven were intestinal. On the other hand the spleen, which by some authors is considered to be always affected, was found free in one third of the cases. The fibrosis is not present in all cases of long duration. There seems to be a relation between age and duration, the chronic forms being more frequent in young patients, acute ones (with less than six months' duration) in older people. The biopsy diagnosis could not be made in seven cases. Moderate leukocytosis with lymphopenia is the rule. Eosinophilia plays no role. Four of the cases are doubtful and may be inflammatory hyperplastic processes of specific nature different from lymphogranulomatosis. Two cases are early, one of them represents an accidental finding of lymphogranulomatosis of the nodes in a man who died of pneumonia. Atypical forms should be studied carefully and collected, but one should not give new names to them. Lymphogranulomatosis is much more frequent than any systemic disease of the lymphatic apparatus. There was one localized blastoma-like granuloma of the intestine. Only fifteen or sixteen cases of the twenty-nine were typical, and they too partly looked uncharacteristic and gave a variety of histologic pictures. In three instances blastoma-like pictures were found in addition to a typical lymphogranulomatosis. Lymphocytic hyperplasia is not a feature of typical lymphogranulomatosis. Overgrowth of reticulum cells is found in early stages. Plasma cells perhaps develop out of reticulum cells too. For the many details of the paper the reader must be referred to the original.

ALFRED PLAUT

Immunology

BRUCELLA ABORTUS IN MILK SUPPLY AS A SOURCE OF AGGLUTININS IN HUMAN SERA MERRILL J KING and DOROTHY W CALDWELL, Am J M Sc 178 115, 1929

Persons with lowered resistance who drink raw milk infected with *Brucella abortus* may develop agglutinins in their blood serum with or without the manifestation of appreciable clinical symptoms of undulant fever. Of 851 patients and 156 staff members in a sanatorium in which raw milk was used, 91, or 9 per cent, showed abortus agglutinins when their serums were diluted 1:15 or higher. Twenty-four of the ninety-one had agglutinin titers varying from 1 to 45 to 1 to

3,200 The presence of abortus agglutinins in human serum is evidence of infection with *Brucella abortus*. The agglutinins may persist in the serum for months or years after the recovery of the patient. There is complete lack of evidence of porcine infection in our herd. The correlation between the periods of *Brucella abortus* infection of the milk supply and the occurrence of agglutinins in the serums of the patients indicates a bovine origin of the cases of undulant fever reported in this study. *Brucella abortus* may be present in small numbers in the milk of infected cows, but the organisms may be eliminated for several years. The presence of *Brucella abortus* agglutinins in the blood serums of cows does not determine whether they are discharging *Brucella abortus* in their milk. In a herd of 151 animals, no evidence was obtained of the infection of the milk of cows whose serums agglutinate at 1 to 60, while cultures of *Brucella abortus* were obtained from the milk of only 23 of 56 cows with titers of 1 to 120 or higher. *Brucella abortus* was not isolated from the blood or from the urine of the infected cows.

AUTHORS' SUMMARY

ALLERGIC PURPURA H. L. ALEXANDER and C. H. EYERMANN, J. A. M. A. **92** 2092, 1929

Cases are described of purpura with abdominal pain following the ingestion of particular foods.

COTTONSEED AND KAPOK SENSITIZATION G. T. BROWN, J. A. M. A. **93** 370, 1929

Cottonseed and kapok ("silk floss") may give rise to apparently specific sensitization in the form of asthma and other allergic reactions. The cotton plant and the kapok tree are related. It is recommended that patients with nonseasonal allergy be tested with cottonseed protein.

SKIN HYPERSENSITIVENESS OF PATIENTS WITH RHEUMATIC FEVER AND CHRONIC ARTHRITIDES TO FILTRATES, AUTOLYSATES AND BACTERIAL SUSPENSIONS OF STREPTOCOCCI KONRAD E. BIRKHAUG, J. Infect. Dis. **44** 363, 1929

A series of 3,114 skin tests was performed during the summer of 1928 in European clinics on 594 persons among whom were 42 active and 146 inactive or "cured" cases of rheumatic fever, carditis and chorea, 69 cases of chronic infectious and degenerative arthritides and 337 nonrheumatic controls.

An excessive universal hypersensitiveness (allergy) was found among 68 per cent of all types of acute rheumatic fever infection to the filtrates, autolysates and bacterial suspensions produced by the indifferent nonmethemoglobin-forming streptococcus and *S. viridans*, while only 22 per cent reacted to the filtrates and 36 per cent to the autolysates and bacterial suspensions produced by the hemolytic streptococcus.

Hypersensitiveness to nonhemolytic streptococcal products is most marked among active cases of rheumatic infection (72 per cent); these cases react almost equally well with filtrates boiled for four hours (67 per cent), while 64 per cent of inactive cases react to nonhemolytic streptococcal products and 25 per cent to the boiled filtrates. Only 33 per cent of patients with active and 29 per cent of those with inactive rheumatic fever react to hemolytic streptococcal products, while 25 per cent of the nonrheumatic controls react to the hemolytic and 14 per cent to the nonhemolytic streptococcal products.

Among a series of 69 cases of chronic arthritides, 53 cases were due to infectious processes, and 47 per cent of these reacted markedly to the products of both nonhemolytic and hemolytic streptococci.

It appears that a nonspecific, common allergenic factor is present excessively in the bacterial products of indifferent and viridans streptococci and moderately

present in solutions of hemolytic streptococci, to which patients with either acute rheumatic infections or chronic infectious arthritides react hyperergically

AUTHOR'S SUMMARY

SKIN REACTIONS TO FILTRATES AND KILLED CULTURES OF GREEN-PRODUCING COCCI IN RELATION TO MEASLES WILLIAM L BRADFORD, J Infect Dis 44 378, 1929

No definite relationship was found to exist between the immune and non-immune to measles as determined by cutaneous reactions to the toxic filtrates and antigens of certain green-producing cocci, including the Tunncliffe coccus, the organism of Duval and Hibbard and *Streptococcus morbilli* of Ferry

AUTHOR'S SUMMARY

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI JAMES M NEILL AND WILLIAM F FLEMING, J Infect Dis 44 397, 1929

The hypersensitiveness described agreed with the previous example of diphtheria hypersensitiveness in two respects there were immediate skin reactions to either diphtheria or xerosis diphtheroid material, and the hypersensitive reactivity could be transferred to local skin areas of normal persons The two states of hypersensitiveness were not identical however The first distinction was that the ratio of diphtheria reactivity to xerosis reactivity was different for the two persons, the one being more reactive with the xerosis diphtheroid than with diphtheria, the other being more reactive to diphtheria than to the diphtheroid The second distinction was that the one was reactive with a heat stable constituent of the diphtheroid filtrate while the diphtheroid constituent to which the other person reacted was heat labile Although both persons gave the same type of skin reaction to both the diphtheria and the diphtheroid bacteria, the described distinctions suggest a difference in the bacterial origin of their sensitization

AUTHORS' SUMMARY

PASTEURELLA PESTIS DETOXIFIED WITH FORMALDEHYDE FOR IMMUNIZATION AND AGGLUTINATION TESTS A BATCHELDER, J Infect Dis 44 403, 1929

Pasteurella pestis antigens prepared with 0.85 per cent sodium chloride solution containing a diluted solution of formaldehyde U S P (1:25) are killed within seven to eight hours The suspensions are smooth and stable Immunization of laboratory animals for the production of agglutinating serums may be readily accomplished by giving a small number of large intravenous doses of such antigens in rapid succession The serums so produced are of moderately high titer but highly specific The agglutination reaction with suspensions and serums produced in this manner is of the readily visible, flocculent type

AUTHOR'S SUMMARY

ISOHEMOLYSINS CORNELIA M DOWNS, H P JONES and KENNETH KOERBER, J Infect Dis 44 412, 1929

Isohemolysins were present in 65.9 per cent of the serums from white persons and in 49.5 per cent of the serums from Indians The failure of hemolysin in the fresh serums tested seems to be due to the absence of hemolysin rather than of complement Only a small percentage of the serums may be reactivated after heating by the addition of complement This is due to masking rather than to destruction of the hemolysin A distinct but not type-specific inhibitory effect could be demonstrated by the addition of heated serum to the active serum and cells Isohemolysins behave like natural heterohemolysins and immune heterohemolysins in regard to absorption by their specific cells in the cold and their dependence on complement No concentration by precipitation methods could be demonstrated No hemolysin for corpuscles containing the C factor could be demonstrated No hemolysis or agglutination was observed in testing serums of groups A, B, and AB against cells of group O

AUTHORS' SUMMARY

CUTANEOUS IMMUNIZATION AGAINST THE STREPTOCOCCUS OF GUINEA-PIG LYMPHADENITIS L D HERTERT and K F MEYER, J Infect Dis **44** 489, 1929

The streptococcus of guinea-pig lymphadenitis has been used in the study of local immunization leading to the following conclusions no protection could be demonstrated by means of Besredka filtrates, the portal of entry could not be closed by means of single or multiple injections of heat-killed streptococcic vaccines and no local nonspecific resistance could be induced by intradermal injection of sterile broth or salt solution

AUTHORS' SUMMARY

CUTANEOUS IMMUNIZATION AGAINST *B. AERTRYCKE* IN THE GUINEA-PIG HAROLD L AVERILL and K F MEYER, J Infect Dis **44** 495, 1929

The intracutaneous injections of sterile antiviral containing specific filtrates may protect guinea-pigs within twenty-four hours against a fatal intracutaneous injection of highly toxic *B. aertrycke* in the same area Some protection may be secured by subcutaneous injection of antiviral provided the massive infective dose is introduced not sooner than from forty-five to seventy-two hours after treatment Similar experiments with Friedlander's bacillus and *Vibrio septique Clostridium chauvæi*, gave negative results

Guinea-pigs are protected on the eighth to tenth day after intracutaneous injections with specific filtrates or vaccines against subcutaneous or oral infections These experiments indicate that the skin possesses special immune biologic properties for bacteria

AUTHORS' SUMMARY

HEMOGLOBINURIA AND URTICARIA FROM COLD KENNETH E HARRIS, THOMAS LEWIS and JANET M VAUGHAN, Heart **14** 305, 1929

Hemoglobinuria occurring in response to exposure to cold was found to be due to an hemolysin in the patient's serum The skin reaction following the exposure was caused by a dermolysin in the patient's blood which at low temperatures united with the skin cells causing increased permeability and discharge of their contents This is similar to what happens to the red blood cells in producing hemoglobinuria Possibly certain cases of Raynaud's disease should be included in this category, gangrene being due possibly to a more intense action of the lysin on the skin The dermolysin and hemolysin may occur singly or in combination as do also the hemoglobinuria and the urticaria

PEARL ZEEK

THE MEINICKE REACTION IN CONVALESCENTS FROM DIPHTHERIA H HENTSCHEL and L SZEGO, Klin Wchnschr **8** 1395, 1929

Micro-Meinicke reactions in children with diphtheria became positive by the eleventh to fifteenth day following antiserum injections in 81 per cent of the serums tested There seems to be no relation between such positive reactions and serum sickness Positive Meinicke reactions have been observed also with other diseases following serum injection The serum reactions become negative gradually after several weeks Other serologic tests for syphilis such as the Wassermann and the Sachs-Georgi react in much the same way following immune serum injections

EDWIN F HIRSCH

DIPHTHERIA IMMUNIZATION WITH TOXIN-ANTITOXIN FLOCCULES ACCORDING TO H SCHMIDT MAX SOLDIN, Munchen med Wchnschr **76** 1208, 1929

Children are rendered immune toward diphtheria by a single injection of 1 cc of toxin-antitoxin floccules For nurslings 0.5 cc at the age of 6 months is recommended

AUTHOR'S SUMMARY

IMMUNITY AGAINST TUBERCULOUS SUPERINFECTION B LANGE AND K LYDTIN,
Ztschr f Hyg u Infektionskrankh **110** 209, 1929

By the inoculation of minimal doses of a certain strain of attenuated tubercle bacilli it was possible to produce in a guinea-pig with great regularity a form of tuberculosis which remained local for a long time Guinea-pigs that had been prepared in this manner showed a certain degree of protection against superinfection with minimal doses of virulent bacilli if the superinfection was produced five weeks or later after the primary infection The protection was greater than that afforded by cultures B C G of Calmette, but it was less than that afforded by previous inoculation with a virulent strain of tubercle bacilli It seemed as if the protection was proportional to the degree of tuberculous disease that was present in the inoculated animals In either case the resistance produced was only a slight one

W OPHULS

ON THE AGGLUTINOGEN PRODUCED FROM RED CORPUSCLES BY BACTERIAL
FERMENT V FRIEDENREICH and T THUNE ANDERSEN, Acta path et
microbiol Scandinav **6** 236, 1929

The specificity of this agglutino-gen, which was discovered by Thomsen, is confirmed It has been demonstrated in the corpuscles of all the species examined and also in certain of the organs It is regarded as a newly formed substance—receptor T—and its relation to iso-agglutination is discussed

Tumors

MALIGNANT EPITHELIAL TUMORS OF THE NECK OF UNKNOWN ORIGIN J E
MCWHORTER, Ann Surg **90** 1, 1929

Twenty-four cases of tumors about the angle of the jaw furnish the subject of this article The masses are described, grossly, as firm, smooth or lobulated and usually encapsulated tumors situated in the deep tissues with freely movable skin overlying them Histologically, they are composed of more or less undifferentiated epithelial cells which are similar to squamous epithelium but are frequently of a more embryonal type An alveolar arrangement or a tendency to form sheaths of varying widths is not an unusual picture They are frequently diagnosed as Hodgkin's disease or lymphosarcoma No cysts are found and therefore the author concludes that they are not of branchiogenic origin The usual tumors involved in this differential diagnosis are discussed

RICHARD A LIFVENDAHL

THE EFFECT OF PARATHYROID HORMONE AND INCREASED CALCIUM METABOLISM ON THE GROWTH OF TUMOR TISSUE A GOERNER and B J P
SHAFIRROF, J Cancer Research **12** 294, 1929

The effect of parathyroid extract and increased serum calcium has been studied on the growth of Flexner rat carcinoma and the Crocker Fund sarcoma no 10 The calcium content of the Flexner tumor has been increased but no inhibitory effect due to calcium was effected The growth chart, which shows the tumor to be rapidly growing, and three cases of metastases are recorded The calcium content of sarcoma no 10 has not been increased—no difference of growth from the control being recorded

AUTHORS' SUMMARY

THE CARBOHYDRATE METABOLISM OF TUMORS (GLYCOLYSIS OF TUMOR TISSUE
IN THE LIVING ANIMAL) C F CORI and G T CORI, J Cancer Research
12 301, 1929

Cori and Cori report their experiments on glycolysis (the splitting of dextrose into lactic acid) of tumor tissue in vivo Their ingenious technic was given in a

previous paper. In brief, a sarcoma was established on one wing of a chicken, and the venous blood leaving the tumor was compared with the venous blood from the normal wing. The blood that had passed through the tumor contained on an average 16 mg per cent more lactic acid and 23 mg per cent less dextrose than the blood that had passed through the tissues of the normal wing. Once this fact was established, they attempted to determine the rate of lactic acid formation of the tumor in the living animal in a quantitative way. They have obtained the following results. Rats with tumors weighing from 14.2 to 21 per cent of their body weight showed a marked increase in the lactic acid content of the blood. When the tumors corresponded to less than 10 per cent of the body weight, the lactic acid content of the blood was within normal limits.

They also found that the intravenous lactic acid tolerance of tumor-bearing rats was decidedly lower than that of normal rats and the decrease in tolerance was fairly proportional to the size of the tumor. By determining the difference in the lactic acid tolerance between normal and tumor-bearing rats, it was possible to arrive at an estimate of the rate of lactic acid production of the tumor tissue in the living animal. The values obtained varied between 570 and 800 mg of lactic acid per gram of fresh tumor per hour, with an average of 690 mg. It is interesting that the rate of glycolysis of the tumor *in vivo* depends on the blood sugar concentration. At a normal blood sugar level of the tumor-bearing animals the glycolysis corresponds to one-half the maximal possible glycolysis of the tumor. The intravenous dextrose tolerance of tumor-bearing rats is the same as that of normal rats.

B. M. FRIED

A. CYSTICERCUS CARCINO-OSTEOCHONDRO-SARCOMA OF THE RAT LIVER WITH MULTIPLE CYSTICERCUS SARCOMATA. F. D. BULLOCK and M. R. CURTIS, *J. Cancer Research* **12** 320, 1928.

Bullock and Curtis were the first to note that when rats are fed with *Cysticercus fasciolaris*, the larva of the cat tapeworm, *Taenia crassicolis*, they develop malignant connective tissue tumors of the liver. No adequate hypothesis has as yet been proposed to explain the lack of response on the part of the hepatic cells or the bile duct cells to form new growths under the influence of the same parasite. This is the more interesting in connection with the fact that in man *Paragonimus* frequently causes hepatic cancers.

In the present paper, the authors report a detailed study of a chondroma or chondrosarcoma and of a mixed tumor which they found in a rat infested with *Cysticercus fasciolaris*.

B. M. FRIED

LOCAL INJURY AS A POSSIBLE CAUSATIVE FACTOR IN SARCOMA. E. BRADLEY, *Brit. M. J.* **1** 599, 1929.

A railway signalman, aged 45, was well on April 19, 1928, when he pulled over a heavy signal lever with his left hand while his head was turned fully to the right, he felt something snap in the left side of his neck and had severe pain. On April 21, a physician noted a tumor, the size of a hazelnut, under the middle of the left sternomastoid muscle. The tumor increased rapidly in size but the man worked until May 4. On May 13, there was a brawny induration of the left side of the neck from the mandible to the clavicle and from the larynx to the edge of the trapezius muscle. On May 24, an operation was performed in an attempt to relieve the pressure on the larynx, death from cardiorespiratory failure occurred twelve hours later. At autopsy an unencapsulated conical mass, 4 inches (10.16 cm) wide at the base and 6 inches (15.24 cm) high, was removed from the neck. Microscopically, it was a highly malignant endothelial sarcoma. The trauma was regarded as a probable factor if not in causing the tumor, at least in having accelerated its growth.

GEORGE RUKSTINAT

ON THE ACTION OF A GENERAL FACTOR IN THE DEVELOPMENT OF TAR CANCER
IN WHITE RATS BRUNO POLETTINI, *Tumori* **3** 306, 1929

On the basis of his personal researches and those of others, the author comes to the conclusion that in causing experimental cancer in rats tar acts not so much as an irritating factor, as by profoundly modifying the general state of the organism of the animal in such a way as to produce a true predisposition to tumor growth

W OPHULS

THE INTERCELLULAR BRIDGES AND THE GENESIS OF CARCINOMA A KREIKER,
Virchows Arch f path Anat **271** 724, 1929

This study is based on thirty-eight cases of basal cell carcinoma of the face. In more than half of them a nevus verrucosus preceded the carcinoma. The usual theories concerning the cancer cell assume a biologic change within the cell which makes the cell a foreigner to the organism. This seems biologically impossible. In the theory brought forward by the author, such an assumption is unnecessary. Carcinoma (of the skin) is formed when isolated basal cells are unable to form a closed system again. Normally, all skin epithelium forms one mechanical system, the cells being united by the intercellular fibrils. When a trauma, for instance, isolates a group of cells, the isolated cells will multiply until they have formed a new system or have become reunited with the skin epithelium. The intercellular fibrils represent the anatomic basis for the growth restraint of skin epithelium. A frequent form of a new closed system formed by isolated skin epithelium is the cyst, it does not grow any more, it only becomes distended. The best example for absence of a closed system is the tissue culture with its unrestrained growth. The fact that in basal cell carcinoma all cells are connected with each other explains the absence of metastasis. The ulceration is due to the absence of the protecting hornified layer, it does not prove the destructive power of the tumor cells.

ALFRED PLAUT

ON TAR CARCINOMA WITH LONG LATENT PERIOD R ZENKER, *Ztschr f Krebsforsch* **28** 121, 1928

In a rabbit that had been subjected to repeated application of tar to the ear over a long period, the initial hypertrophic changes disappeared almost completely after the cessation of the applications, but two years after this there developed the usual tar carcinoma. Evidently, the processes initiated by a temporary irritation may persist with eventual development of malignancy—a phenomenon observed in human beings in the carcinomas of aniline and paraffin workers.

H E EGGERS

CONTRIBUTION TO THE PATHOLOGY OF ATYPICAL GRAWITZ TUMORS F
SCHAFFHAUSER, *Ztschr f Krebsforsch* **28** 131, 1928

On the basis of a fully described tumor of the Grawitz type, apparently primary in the kidney, which showed marked metaplastic development in the form of recognizable tubules, alveoli of vacuolated cells, sarcoma-like portions and giant cells, the writer concludes that the most logical explanation of the so-called hypernephromas is that they originate in undifferentiated embryonic tissues, with potentialities toward both suprarenal and renal development.

H E EGGERS

ON THE TAR CANCERS OF BRIQUET WORKERS TEUTSCHLAENDER, *Ztschr f Krebsforsch* **28** 283, 1929

In a study of the tar cancers of briquet workers made in Baden and South Wales, the author arrives at the following conclusions. The cancers are of the ordinary squamous epithelial type and do not differ in their behavior from similar carcinomas of other origin, the briquet dust appears to be the irritative agent, possibly also the vapors arising in the course of briquet manufacture. These

carcinomas are of frequent occurrence, but seldom appears in less than five years' exposure, after this period tar warts are practically constant. Preventive measures are urged: the preferential employment of young persons, the frequent changing of labor personnel, avoidance of personnel with already diseased or unduly sensitive skin, avoidance of persons who will not observe rules of personal cleanliness or prophylaxis, publication and explanation of prophylactic rules, supervision of their enforcement and moistening of the dust.

H E EGGERS

STUDIES OF THE HISTOGENESIS OF ROENTGEN TUMORS OF PLANTS KOMURO
HIDEYO, *Ztschr f Krebsforsch* **28** 371, 1929

In developing roentgen tumors of the root tips of pea seedlings, the writer describes filiform structures resembling closely what have been described as nerve filaments in experimentally induced tumors in animals.

H E EGGERS

TAR CANCERS IN VITALLY IMPREGNATED MICE J G SANCHEZ-LUCAS, *Ztschr f Krebsforsch* **28** 374, 1929

Tar cancers were found to develop in mice that had been impregnated with India ink by intravenous or intraperitoneal injection, in splenectomized mice and in mice subjected to both procedures, to the same degree as in untreated animals. There were no noteworthy differences shown in the microscopic examination of the internal organs.

H E EGGERS

THE HISTOLOGIC SIMILARITY BETWEEN EPITHELIAL REGENERATION AND
CANCER FORMATION H MUELLER, *Ztschr f Krebsforsch* **28** 383, 1929

The author is an advocate of the theory that epithelial regeneration occurs not from epithelial cells themselves, but from undifferentiated elements originating in close association with subepithelial capillaries. According to his view, carcinoma is the result of repeated destruction of epithelial cells, with liberation from them of hormone-like substances which stimulate the undifferentiated elements to excessive and eventually unrestrained reproduction of the destroyed cells. He believes that he has evidence for the view that metastatic growth is really accomplished by mesenchymal elements stimulated to the formation of epithelial cells by the hormones reaching the new site from the primary location.

H E EGGERS

ON A CASE OF CANCER FOLLOWING A BURN H STAUFFER, *Ztschr f Krebsforsch* **28** 418, 1929

Stauffer reports a case of facial carcinoma following a local burn incurred thirty days before. The surrounding noncancerous skin showed marked senile precancerous hyperkeratosis.

H E EGGERS

SPONTANEOUS TUMORS OF MICE AND THE ETIOLOGIC ASPECTS OF THE CANCER
PROBLEM L HEIDENHAIN, *Ztschr f Krebsforsch* **28** 443, 1929

Since Haidenhein's experimental results have been explained on the basis of spontaneous tumor development, he discusses in this article the incidence of such tumors. In his experimental material, his frequency of tumor development was of the same order as that observed by Maude Slye in her work on the genetics of tumor. Unlike her tumors, those obtained by him showed no particular affinity for certain organs, and a number of them were located in regions in which spontaneous tumors are very rare in the mouse. From such information as he was able to gather, the relative frequency in Germany of spontaneous tumor development in mice is about 14 per cent—a figure far less than that obtained by him experimentally.

H E EGGERS

RESULTS OF THE CYTOLOGIC STUDY OF TUMORS B LIPSCHUTZ, Ztschr f Krebsforsch 28 491, 1929

Using Giemsa's stain in carefully selected material, the writer has found in the cells of Rous' sarcoma intracellular inclusions of the same general order as those found in diseases caused by known filtrable viruses. In view of the numerous other similarities between the filtrable agent of Rous' sarcoma and those viruses, he concludes that the demonstration of these bodies places this agent among the filtrable infections

H E EGGERS

THE DEVELOPMENTAL STAGES OF THE EPITHELIAL CHANGES PRECEDING SKIN TAR CANCERS A BABES, Ztschr f Krebsforsch 28 533, 1929

The precancerous changes in the skin of the rabbit's ear following application of coal tar vary according to the mode of application, one series of changes following the simple swabbing of the surface, another the deep introduction of the tar by rubbing. With the former there is first an atrophy of the hair follicles and sebaceous glands, but with persistence of their surface openings, which dilate into saclike invaginations from which there is an outgrowth of epithelial buds. Between the sacculi there is hypertrophy of the skin, either diffuse or in the form of buds. As the sacs deepen, the skin assumes a papillary surface relationship, without anything atypical in the overgrowth except hyperkeratinization. With the deeper introduction there is complete destruction of hair follicles and glands, with regeneration of these elements in the form of epithelial processes which gradually grow deeper and cornify. There is a great resemblance of these changes to senile hyperkeratosis.

H E EGGERS

Medicolegal Pathology

METHYL CHLORIDE POISONING A H KEGEL, WILLIAM D McNALLY and A S POPE, J A M A 93 353, 1929

This article reviews briefly the literature in question and discusses the symptoms and changes in the organs caused by methyl chloride gas in high dilutions. The interest in poisoning from this gas is acute in Chicago at this time on account of the occurrence of a considerable number of deaths from the escape of methyl chloride gas in kitchenette apartments from leaks in the apartment units. Undoubtedly, instances of poisoning have occurred without being recognized as such. The principal symptoms appear to be drowsiness, mental confusion, nausea, vomiting, coma and, in severe forms, convulsions. The lesions consist of parenchymatous degeneration, multiple hemorrhagic extravasations and pulmonary congestion. The clinical sequelae suggest progressive degenerative processes in the central nervous system.

RECENT ADVANCES IN TOXICOLOGY AND FORENSIC MEDICINE SIR WILLIAM WILCOX, Lancet 2-970, 1927

At a meeting of the Medico-Legal Society of London on Oct 27, 1927, Sir William Wilcox, in discussing some of the ways in which toxicology assists the law, referred at some length to arsenic, the arsenobenzene compounds, the improved methods for detecting alkaloids, the differences in the symptoms of poisoning from lead when given intravenously as is done for cancer, and the usual symptoms of poisoning from this metal, and to the huge number of new drugs, especially the hypnotic remedies and the 257 deaths (from 1905 to 1925) from the barbituric acid group. He also mentioned the liver poisons, tetrachlorethane, trinitrotoluene, dinitrobenzene, picric acid and dinitrophenol, and the toxic jaundice and subsequent cirrhosis that they cause. He also spoke briefly of the advances made in the study of blood stains, particularly blood grouping and the interest recently displayed in Great Britain in wounds from fire-arms, more especially

since Professor Sidney Smith gave so much attention, when in Cairo, Egypt (now in Edinburgh), to the identification of bullets by marks that they receive from the barrels through which they are fired

E R LeCOUNT

INFANTICIDES BEFORE THE INFANTS HAVE BREATHED M E SOREL, *Ann de med leg* 8 515, 1928

There are many reports of infants killed by a kick or blow on the head, strangulation or even decapitation before they had a chance to breathe and with only the head born. As a consequence, pulmonary docimasia, tests to determine whether the child has breathed or not, although very important, are by no means final in deciding whether infants are born alive. Sorel reports two cases of live birth, one of them first known when the mother confessed having killed the infant before it made a noise, by wounding the hard palate with a finger or fingers in the mouth when she suffocated the infant. The other infant was strangled with a strip of ticking and there were hemorrhages in the outer layers of the wall of the left carotid artery where the cord had bruised the vessel. Thorough examinations in various ways failed to disclose any evidence of aeration of the lungs of either child.

E R LeCOUNT

TRAUMA AND TUBERCULOSIS L DESCLAUX, *Ann de méd leg* 8 518, 1928

In order to prevent an awning from falling the left hand of a young girl who was helping lift it was so severely twisted on her forearm that the wrist swelled and was painful. Six weeks later tuberculosis was found of the left carpal bones. A maximum of a year of disability was fixed as the basis of compensation. Discrete lesions with dulness were found in the apex of the left lung. The opinion was given that the bones of the wrist were tuberculous at the time of the accident and the torsion had brought on a more rapid development of the fungous osteoarthritis.

E R LeCOUNT

INFANTICIDES AND ABORTIONS IN WARSAW SINCE THE WORLD WAR W GRZYWO-DABROWSKI, *Ann de med leg* 8 545, 1928

INFANTICIDES IN EUROPEAN RUSSIA N W POPOFF, *Ann de med leg* 8 532, 1928

This is a detailed account full of statistics of the increase of abortions, infanticides and deaths of the mothers from puerperal sepsis in Warsaw in the eight years between 1918 and 1925, also of the apathy of the public and the leniency of the law regarding them. Based on the numbers of abortions in Paris before the war, 50,000 each year for 3,000,000 inhabitants, and those in Lyon at that time, 10,000 a year for a population of 500,000, the number in Warsaw is said to be at least 15,000 for its population of 1,000,000. Calculations from other sources place the abortions in Warsaw as 1 for every 5 pregnancies. The ratio to births for four years is as follows:

Year	Births	Abortions
1921	21,710	4,991
1922	22,980	5,285
1923	22,701	5,451
1924	21,157	4,866

Estimates made from the number of women treated in hospitals for the complications following abortions, the number of postmortem examinations and court statistics all were found corroborative of the increase of abortions and of infanticides.

At the Medico-Legal Institute in Warsaw in these years, from 1921 to 1925, 1,043 bodies of infants born at term or prematurely were examined, 483 stillborn and of these only 13 per cent at term, 142 infanticides or deaths from violence and of these 85 infanticides by asphyxia in one way or another. There were

20 bodies of infants born at term in which cranial fractures were found, 48 were born at term and died solely from lack of proper care at that time, and 117 were nonviable, etc

During the years from 1918 to 1925, examining magistrates inquired into 141 cases of infanticide. In 47.7 per cent the women were acquitted, in 18.5 per cent condemned, but frequently with a reprieve, in 35.7 per cent the accused was condemned for failure to bury the body of the fetus or infant. Among cases tried for abortion from 1920 to 1924 inclusive, the mothers were implicated in 45 and of these women 16 were convicted and 39 set free. There were 51 midwives tried during this same period and 16 were convicted. In higher courts, of 118 who were tried for abortion, 58 were convicted. The deaths of mothers from abortion and its sequences rose steadily from 18 in 1921 to 43 in 1926. Popoff, Professor of Legal Medicine in Smolensk, reckons that the increase in infanticide, defined in Russia as murder of the infant by the mother at the time of birth, increased from 27 per ten thousand births in 1909 to 67 in 1925, the total number being 376 in 1909 and 1,120 in 1925. For the years from 1913 to 1919 inclusive, information is not available.

E R LeCOUNT

INDUSTRIAL DISEASES G ROUSSELIER, *Ann de med leg* 8 553, 1928

In a military pharmacy three employes were found affected by drugs with which they were employed. One was sensitive to quinine and suffered with engorged blood vessels of the head and neck resembling impetigo or an eczema, these were much worse if the patient was menstruating. Another had eczema whenever she worked with emetine, a third woman had eczema from powdered pyrethrum. Another laborer suffered from an acute poisoning from handling crude *nux vomica*, four others painful conjunctivitis from asphalt, and others local lesions from cement used in making tiles. These are all mentioned as unusual disorders from occupations with which the customary legal awards for damage and disability have had, as yet, but little to do.

E R LeCOUNT

EXPLOSION IN A STARCH FACTORY J LECLERCQ, C VALLEE and M MULLER, *Ann de med leg* 8 581, 1928

In describing the conditions accompanying and results from the explosion of a starch factory near Lille in which seven persons were killed and thirty-seven wounded, eight of these severely, the position of some of the bodies is described and illustrated as follows: extremities shrivelled, thighs flexed on the pelvis, legs flexed on the thighs, forearms flexed on the arms, the hands and fingers flexed and in front of the chest in the attitude taken by boxers. The red blood corpuscles in the capillaries of the lungs were found carbonized by a microscopic examination.

E R LeCOUNT

STAINS ON CLOTH MADE BY BLACK POWDER PIEDELIEVRE and SIMONIN, *Ann de med leg* 8 615, 1928

By using crockery ware, shaggy cloth, white linen, sheets of rubber, animal skin, etc., as targets and removing the metal bullets so as to leave simply the powder, it was proved that the black rings with white centers made by black powder shot against certain fabrics are due to a rebound of the cloth. Such marks are not made on the skin, nor are they made by smokeless powder.

E R LeCOUNT

TRAUMATIC DIABETES G ROUSSELIER, *Ann de med lég* 8 617, 1928

Injuries of the cerebrospinal axis sustained by two persons were followed by diabetes. One was a man, aged, 65, who was debilitated, the sugar was never more than 2 Gm in twenty-four hours and disappeared altogether after a few months. There was no glycosuria twenty days before the accident, which among

other injuries included a wound in the right temple, 4 cm long. In the second case, it was admitted that glycosuria might have been present before the accident. Compensation based in some part on traumatic diabetes was secured by both patients. Roussellier mentions about fifty other patients in whom injury was followed by a great variety of definite lesions of the brain, but without glycosuria. He believes that traumatic diabetes is exceedingly rare.

E R LeCOUNT

ASSAULT WITH LIGATION OF THE PENIS P MULLER, *Ann de med leg* 8 620, 1928

A boy, aged 8 years, fearing punishment, managed to keep secret his ligated penis until after departure of his father the next morning, when it was discovered by his mother. It was necessary to call a surgeon to sever the cord deeply buried in the penetrated base of the prepuce. The scrotum and loose tissues about the bladder were infiltrated with urine of which a large amount escaped when the cord was cut. Gangrene for 4 by 7 cm of the scrotum followed, but about three months later the parts were normal.

The boy accused two other boys of attacking him, one of 12 holding him down while the other, about his own age, tied his penis. This the boys denied and they were released from custody. The case was then carried to a higher court, and in spite of an opinion given by Muller that the boy could not have tied his penis in the way it was found, they were again released. The report illustrates the difficulty of legal dealings with children. In discussing this, Brisard told of complete severance of the urethra from a ligature of the base of the penis of a boy of 7 or 8 years which the boy himself had applied.

E R LeCOUNT

DEATH FOLLOWING PUNCTURE OF THE CISTERNA CEREBELLOMEDULLARIS, H STEINDL, *Deutsche Ztschr f Chir* 209 97, 1928

In place of obtaining colorless, thin, cerebrospinal fluid when the cisterna was punctured to relieve pressure, blood poured forth in a pulsating stream and after death the left vertebral artery was found punctured. From the perforated artery blood accumulated beneath the dura at the base of the brain. A carcinoma of the pharynx had invaded the brain and although trephining, and also many lumbar punctures, had already been done to relieve pressure, it was thought that puncturing the cisterna would relieve the headaches. The artery was wounded because the cisterna was empty and the medulla was displaced back and to the right bringing the left vertebral artery into the line of puncture. Death did not occur until four days after the puncture.

E R LeCOUNT

ANEURYSM OF THE AORTIC ARCH FOLLOWING A WOUND WITH SHRAPNEL R NISSEN, *Deutsche Ztschr f Chir* 211 262, 1928

Shortness of breath, considerable expectoration and subcutaneous emphysema all appeared rather abruptly two weeks after a man, aged 36, was wounded with shrapnel in 1916. The ball entered behind between the shoulder blades. During the third week, a left thoracentesis yielded blood and there were abnormal heart sounds affecting all the valves. He returned to the war front in 1917, and to his occupation as carpenter after the war. Because of pain in the thorax, an examination in 1920 revealed the shrapnel ball, and he obtained 20 per cent of the total disability pension. His work was not heavy for three years after this, but he returned to his carpenter work at the end of this period whereupon the former symptoms returned. In 1927, his pension, then 30 per cent, was considered again and by another examination an aneurysm was found at the aortic arch, the shrapnel ball in the posterior mediastinum moving with each heart beat, the pension was increased to 66 66 per cent.

E R LeCOUNT

SUICIDE AS A RESULT OF BODILY SUFFERING K MEINER, Deutsche Ztschr f d ges gerichtl Med **12** 133, 1928

To refute the rule that persons who kill themselves are mentally diseased two suicides are reported of persons who, it is assumed, were in great pain at the time. In the body of one, death by stabbing, a fresh coronary thrombosis was found, in the other, a perforated gastric ulcer with peritonitis, death by shooting.

E R LeCOUNT

CONCERNING KNIFE WOUNDS H MERKEL, Deutsche Ztschr f d ges gerichtl Med **12** 137, 1928

This is an entertaining account of unusual experiences with stab wounds and of the exceptional peculiarities such wounds may possess. Of three deaths caused by falling on or against knives accidentally, one was of a man who carried a naked knife in one hand and had a fall when riding a bicycle through woods where he feared he might be waylaid. Cuts across the throat, causing the death of a girl, aged 15 years, were obviously made from the left side. It was known that she was right-handed but further inquiry and another examination of the body disclosed that her right hand had been injured some days before. The first suspicions of assault and murder were then dismissed. Some time subsequently, the father admitted that he had punished her for remaining out late just before she had cut her throat. The weapon, a razor, was found by her head and it was concluded from the way the blood was distributed on her clothing and surrounding objects that she inflicted the wounds while kneeling.

Three deaths from stab wounds, deeper than the length of the blades with which they were made, were explained by the force used which drove in the outer parts after they were pierced. In a fourth, the discrepancy between the two, length of blade and depth of wound, was too great and further search resulted in finding a second weapon with a longer blade and its identification as the one used. The most remarkable of the ten cases reported deals with the dead and greatly decomposed body of an unknown woman found in a thicket. A meshwork of vegetation had grown through some of the clothes. When identification was made and it was decided that cuts into the front of the body of the third cervical vertebra represented the bottom or deepest part of wounds across the throat when she was murdered, the affair was easily terminated. She had disappeared about a year previously. The apprehended murderer confessed and was sentenced to death, but subsequently this was changed to imprisonment for life.

E R LeCOUNT

IDENTIFICATION FROM PORTIONS OF BODIES RAESTRUP, Deutsche Ztschr f d ges gerichtl Med **12** 176, 1928

This prosaic account, illustrated by a number of cases, deals with mistakes in the identity of dead bodies, disputes over the identity and the unreliability for purposes of identification of clothing, letters, laundry marks and similar objects found on or with bodies of persons unknown. Publicity of descriptions and photographs of such bodies are the best means of securing identification. Raestrup describes at considerable length measures which when taken result in lifelike photographs. Substances may be injected into the loose orbital tissues to push the eye balls forward, gritty powder underneath the eyelids will hold them open, the sagging mandible may be held forward by sewing the jaws or teeth together in front, and entire faces with glass eyes may be built up from merely the bare skull. Considerable difficulty is met with in identifying burned bodies, but even with these identification is often successful from tattoo marks, matters of dentistry and sometimes finger prints.

E R LeCOUNT

ACCIDENT OR HEART DISEASE W BRANDIS, Med Klin **24** 424, 1928

After opposing expert opinions were obtained from professors in two pathologic institutes, it was decided by officials who pass on matters of insurance for the

government that an occupation was not responsible for the death of a man, aged 48, who died from heart disease. In his work he had occasion to press against machinery with his chest and calluses formed where the upper right ribs join the sternum. The enlarged heart was not explained satisfactorily either during life or after the postmortem examination. The coronary arteries were sclerosed, no mention was made of blood pressure or of histologic examination of the myocardium.

E R LeCOUNT

CHRONIC BENZENE POISONING ONE DEATH K LANDÉ and L KALINOWSKY,
Med Klin **24** 655, 1928

An eczema of the hands and arms, slight changes in the blood, hemorrhage from the nose and gums and later a severe degeneration of the left median nerve with atrophy of the muscles it supplies were the chief symptoms of a man exposed to the vapors of benzene where as many as 15,000 or 20,000 liters were transformed from tanks to cars, his hands were also kept wet with the benzene. The illness occurred after he had this occupation for one year.

The other man worked for two years, applying to automobiles lacquer or varnish in a 40 per cent solution of benzene. His symptoms came on with weakness for about six months before death, loss of appetite and emaciation, and later, hemorrhage from the nose so severe that he finally came under medical observation. At this time the hemoglobin was 36 per cent, but before death it sank to 17 per cent, the red cells numbered only 1,000,000. He also had fever, which has been noted a few times in other patients, with chronic benzene poisoning and has been laid to tissue destruction.

He lived only eight days after entering the hospital, and at postmortem examination the bone marrow was found to be aplastic. Both these patients had a mild leukopenia, gingival hemorrhages and severe bleeding from subcutaneous blood vessels after trivial bruising. The authors claim that the monoplegia is the first to be reported from benzene.

E R LeCOUNT

FATAL HEMORRHAGE FROM A MINUTE ULCER OF THE STOMACH H NAUMANN,
Med Klin **24** 935, 1928

A woman, aged 22, after a few prodromal symptoms diagnosed as mitral insufficiency, had bleeding from the stomach and bowel which was unexplained during life and after death until by careful search a minute gastric ulcer was found with an eroded thrombosed artery stump in its center, the vessel being about as large as a fine hair.

The bleeding continued over at least seven days, but probably lasted much longer because when she first came under observation the hemoglobin was only 36 per cent, just before death it was 17 per cent. There was no evidence of the ulcer in the outside of the stomach, and for this reason an operation probably would have been of little use.

E R LeCOUNT

COMPLETE TEAR OF THE RIGHT SUBCLAVIAN ARTERY IN TRAINING FOR
ATHLETIC SPORTS W KOCH, Med Klin **24** 1473, 1928

A man, aged 22, an all-round athlete, suffered from pain in his right shoulder and chest after swimming with a breast stroke. After a physician had massaged his heart, for he had an hypertrophied heart with some mitral insufficiency, he exercised at home with an "Expander" loaded with a weight of 110 pounds. During this exercise, he was suddenly seized with severe pain as before in the right shoulder and right side of the chest, which also extended down the right arm, soon after, nausea, difficulty in swallowing and air hunger obtained.

He collapsed suddenly on the street five days after return of the pain, became unconscious and was taken to a hospital where at first perforated gastric ulcer was diagnosed. This was abandoned when 600 cc of blood was removed from

the right pleural cavity, death occurred eight days later in the hospital very suddenly after a cry and the appearance of a bluish swelling in the right infra-clavicular fossa and adjacent arm. After death the right subclavian artery was found torn completely across, 3 cm from its origin, and the blood after dissection of the surrounding tissues had broken into the right pleural cavity where there was still 1 liter. Nothing is said by Koch regarding a cervical rib in his difficult explanation of how the tear was produced.

E R LeCount

HEART DISEASE AND ACCIDENT W HEIMANN-HATRY, Med Klin **24** 1596, 1928

A woman who had fallen when 4 years of age and as a consequence suffered for many years from kyphoscoliosis of the spine and a deformed thorax, when 54 injured her chest in an automobile accident, breaking some ribs and one forearm. Directly after the accident she had symptoms of severe cardiac disorder: cyanosis, rapid pulse, many extrasystoles, a sense of cardiac compression and of impending death. She died unexpectedly about seven months later, a necropsy was not done. The opinion is expressed that the internal injuries hastened death from heart disease in one already greatly afflicted with compressed thoracic viscera.

E R LeCount

ACCIDENT, HEART DISEASE OR RENAL DISEASE W BRANDIS, Med Klin **24** 1633, 1928

This is a review by one of the officials, a judge, who decide questions of liability for insurance of employes and includes the observations and opinions of the physicians attending the deceased, as well as the reports of directors of two pathologic institutes whose expert opinions were sought. Claim by the widow for compensation for the death of her husband was denied because the disease of the left kidney from which it was alleged death had resulted was part of a systemic infection and not due to accident.

The man complained of pain and of having torn some muscle of the abdominal wall when lifting a heavy piece of iron. A few days later he died of an infection, thought at one time to be "grippe". At postmortem examination, a thrombo-ulcerative aortic endocarditis was found with embolic hemorrhages and infarcts in both kidneys and the spleen. The head was not opened, the renal lesions were multiple small infarcts and hemorrhages and included no abscess, as was claimed.

E R LeCount

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Oct 14, 1929

HENRY C SWEANY, *President, in the Chair*

THE NECROPSY IN MEDICAL EDUCATION AND STUDY PRESIDENT'S ADDRESS HENRY C SWEANY

I wish to thank you for honoring me as you have on this the fiftieth year of the founding of the Chicago Pathological Society

Custom dictates an address on this occasion I have therefore prepared a discourse on pathology as a basic medical science, the purpose of which is to point out the deficiencies existing in our medical education, resulting from our relative lack of necropsy material

I shall first scan a few centuries of medical history for fitting precedents Beginning with the Renaissance period, relatively few of the outstanding characters need be mentioned to reveal the relationship of morbid anatomy to the progress of medical science Before morbid anatomy could be studied, there had to be a knowledge of normal anatomy

Vesalius (1514-1564), champion of anatomic dissection, boldly departed from Galenic dogma and the theories of his teachers to carry out his classic anatomic studies Nevertheless, he laid the foundation of surgery which Pare, his contemporary, appreciated and made use of to help elevate medicine from the mediocrity of the barber

Enthusiasm then waned gradually until the appearance of John Hunter in the eighteenth century, when a new impetus was given to all branches of medicine As an experimenter in medical research, Hunter knew no limitations His ambition was the solution of the unknown, whether in man or animal, in the field of anatomy, physiology, medicine or surgery However, his greatest accomplishments were in surgery and experimental pathology

Again, on the continent, at the end of the eighteenth century, anatomy and surgery received another stimulus as a result of the efforts of Bichat (1791-1802), a protege, student and friend of the surgeon Desault, whose chief claim to immortality is that he was Bichat's teacher

During this time, internal medicine was plodding along as a semimystic cult, aided at first by the bombastic Paracelsus, but aroused completely by the immortal discovery of Harvey in the early seventeenth century Two hundred years later saw it definitely established on physiologic principles by that versatile genius and teacher, Johannes Muller

Even while surgery was being founded, through anatomic discoveries and internal medicine established on principles of physiology, a new science came into being This afterwards became known as pathology, a synonym more practical but less expressive than the older morbid anatomy

The first great work in this field, entitled "The Seats and Causes of Disease Investigated by Anatomy," by Morgagni, was published in 1761, more than 100 years after Harvey This marked the true beginning of pathology in science In the same year of Morgagni's publication, there was born a Scotchman, Matthew Baillie, who published the first complete textbook on pathology, and included case histories along with the autopsy records

The scene again shifted to France where Bayle, Laennec and others created a lasting medical atmosphere by combining clinical manifestations with anatomic aberrations Again utilizing morbid anatomy as a basis, Bright, Addison and Hodgkin markedly advanced the cause of medicine in England This was followed

by the creation of the Viennese school by Rokitsansky, the pathologist, and Skoda, the clinician, whose combined influence created in Vienna one of the world's greatest medical centers and marked the climax of gross pathologic study

Both medicine and surgery now veered into this new field of morbid anatomy for advancement. Following the cell theory of Schleiden and Schwann and the discoveries of the first great histologist, Henle, microscopic pathology became a field for exploitation. This was ably accomplished by the incomparable Virchow. Rudolph Virchow was the most conspicuous figure in the history of medicine of the second half of the nineteenth century, the most successful exponent of scientific methods of medical investigation and research, and the founder of modern pathology.

With his work, so-called "dead house" pathology became and remained the single most important means of medical education. It is the primary school of medicine, contributing the knowledge that furnishes the foundation for medical education. By it the practice of medicine has been lifted out of a tangled mass of superstition and cultism and established on the basis of an exact science.

During the latter part of this brilliant naissance, the Chicago Pathological Society had its modest beginning, an outgrowth of the West Chicago Medical Society. The first meeting was held in the "Old Washingtonian Home" May 13, 1878, Dr. Norman Bridge presiding. Three years later, it received its present name.

Among the reports of the society printed in the *Chicago Medical Journal and Recorder* of that time, were some by Christian Fenger, the first pathologist at the County Hospital and one of the first modern pathologists in America. In discussing this subject, Kektoen quoted from a report by Dr. Edward Holmes that the first autopsy performed in this part of the country was done by Fenger. Fenger, who had come from abroad, was implanting in the minds of medical men of this community the methods of the European schools. In fact, great pilgrimages to the European clinics began shortly after. It was during this time that Belfield brought back Koch's method for the demonstration of tubercle bacilli.

In the early nineties, laboratory methods were introduced and from that time the reports became more scientific. The "Society Transactions" were started in 1894, and the meetings were held in the central part of the city.

The development of pathology in Chicago proceeded under the industrious efforts of Hektoen, LeCount, Zeit, Klebs, Weaver, Herzog and later Wells, Davis and many others who carried on the work started by Fenger.

Most of our accomplishments, however, have not been in the fields that made Europe the center of medical learning. Bacteriology, under Pasteur, Klebs and Koch, drew a great deal of interest, while immunology, biochemistry and experimental pathology progressed with great strides in this country.

The pathological institutes, so prominent in Europe, have not fared so well. With the exception of LeCount's extensive necropsy experience, the volume of work in Chicago is not to be compared with that in Europe. LeCount's work in the Cook County coroner's office was chiefly suitable for individual study of pathology. By no means do I wish to detract from the unparalleled work in the newer sciences in this country, but I do hope to emphasize the advantage possessed by men who have enjoyed an extensive postmortem training in their medical education, and further emphasize that such training here, except in a few institutions, is far from satisfactory.

Despite the fact that necropsy work has more than doubled in Chicago in the last ten years, the number is far below that obtained abroad. The percentages for the year 1926, from the report of the Institute of Medicine, reveal that the necropsies by permission, not counting the necropsies in the County Hospital, represent 21.1 per cent of all deaths in the respective hospitals, while the figures from the *City Health Bulletin* for the same period, covering all deaths in the City of Chicago, give by calculation only 5.3 per cent necropsies by permission, that is, for every five deaths in the hospitals and every eighteen deaths in the city at large, there is one necropsy by permission. The New York Academy of Medicine reports that the ratio of necropsies done in hospitals in Europe to those in America is as 62.7 per cent to 7.3 per cent, almost 9 to 1, while Karsner places the number for the country at large at 0.7 per cent.

Different authors comment on these statistical variations, here and abroad, from several viewpoints. Lack of interest by physicians is considered the most important. Robertson cited a medical student who hoped that he would not be insulted by being asked for a necropsy on his deceased father. The same author maintained that this feeling is quite general among members of the medical profession. Smith stated that the laity at times are more appreciative of necropsies than physicians. Bell, Wilson and others are in general accord with these statements.

Pathologists especially should be willing to have themselves or members of their families examined postmortem, but unfortunately they do not all set this precedent. This is inexcusable, and Mills said that a conscientious physician has no moral right to ask permission for that which he would not permit for himself or a member of his family.

The causes of this condition vary with the reactions of different physicians, and may be grouped into four divisions. Some do not feel the need of a repetition of the pathologic observations on which they base their clinical diagnosis. For this class, it is well to point to the figures of Karsner which showed that, in a high class hospital, there were 8 per cent gross errors with 60 per cent minor errors, and those of Cabot who reported 47 per cent of diagnoses partially or wholly wrong, over a ten year period, in the Massachusetts General Hospital, also those of Oertel from a large public hospital where only 22.3 per cent of the diagnoses were entirely correct. Frances Carter Wood pointedly summarized the situation in saying that only the pathologist realizes how many patients with hysteria have tumors of the brain, in how many cases of heart disease there are no valvular lesions but nephritis, and that 10 per cent of all old people die of unsuspected cancer.

Another type of physician fears exposure of his ignorance. This class needs no comment further than that a few postmortem examinations in their earlier education would have better prepared them.

In the third group are those too busy or too mercenary to be troubled with postmortem examinations. For their benefit, let us point out that Sir William Osler, among other great physicians, cancelled all appointments to attend necropsies on his patients.

Finally, a fourth group are disinterested or indifferent. Here the pathologist is chiefly to blame. The postmortem service can be sufficiently attractive to interest any physician interested in improving his professional knowledge. The pathologist should gage his success not by the variety of material appearing before him, but by the increasing interest manifest in attendance and number of necropsies.

Next to the apathy of physicians is the lack of appreciation on the part of the public. A difference of opinion exists regarding the cause of popular objection to postmortem examinations. Wilson called it a lack of selfish interest on the part of the relatives to know the condition of the deceased as well as the light it may throw on the condition of the whole family. The reports of the New York Academy of Medicine lay it at the door of ignorance of the value which this procedure has for science and, therefore, for the human race. Consequent on this there is a universal lack of appreciation on the part of the American public.

This general feeling may be resolved into its elementary factors, most important of which is the "emotional." At the time of death, the high state of emotionalism in the family is not given consideration by the physician or the pathologist, to whom a necropsy is only a perfunctory task. This familial sentimentality is present and must be encountered in a sympathetic and tactful manner.

To the emotion of love, there is added a certain amount of fear that has been frequently attributed to religion. There still lingers in the minds of many people the medieval superstition about the dead.

So far as religious objection is concerned, it seems that this, *per se*, has been overemphasized. This attitude of fear concerning religion has no true foundation in any religious code, and nowhere can such reference be found. Personally, I have always found cooperation on the part of the clergy after a few words of

explanation Bluestone, discussing this subject, insisted that religious objections are not hard to refute He cited Father Moulmier, president of the Catholic Hospital Association for 1926, who pleaded for necropsies in hospitals and for the advantages gained from them Although Schultz, Joslin, Karsner and others reported on the difficulty of obtaining permission for necropsies on Jewish patients, it seems more logical to assign the cause to familial ties than to religion

Aside from the apathy on the part of the physician and the ignorance and emotionality of the public, a third and most important factor is the undertaker In some communities, namely Minneapolis and Cincinnati, much assistance has been gained through the cooperation of the undertakers Or they may hinder, as in Chicago and New York

Bell of Minneapolis stated that confidence has been obtained by the correction of the objections and by the education of the undertakers Accordingly, embalming schools have been established in connection with the state university where embalmers learn to prepare bodies on which autopsies have been done Furthermore, the pathologists are careful to leave the vascular system suitable for embalming and refrain from making incisions on the body that show after it is dressed for burial This cooperation has stimulated the undertakers to assist in gaining permissions for postmortem examinations

Janeway cited other complaints by the undertakers, such as undue waiting for bodies, unkind treatment by attendants, undue mutilation by inexperienced men, delay in signing death certificates, etc I am convinced that the example of Bell and Wooly may be followed profitably in Chicago I am so deeply concerned about this subject that I feel we should take active steps toward improving the situation

No systematic attempt has been made to educate the undertaker to an appreciation of the value of the necropsy to humanity Some will not listen, of course, but ultimately they will react the same as those in other cities, with corresponding efforts on the part of the medical leaders No attempt has been made to insure the undertaker against discrimination or collusion Neither has any serious attempt been made to teach the embalming of bodies on which autopsies have been done In fact there has been little in common between pathologists and undertakers, except enmity Although our cause is altruistic and just, such may not be obvious to them, who are only business men We must aid in every way possible to terminate a feud that has done and still is doing so much injury to science

In recommending a solution of this problem, it seems to me that there is one course to pursue, that is, tactful publicity Education will do more than any one thing To improve the situation such education, to be effective, must be shown to benefit the physicians, public leaders, the general public and undertakers

For the physicians there must be greater emphasis placed on the value of necropsies There must be a greater effort and more dignity placed in this work by pathologists In this way, pathologists will live down the popular impression that classes necropsies with anatomic dissection Every physician should be taught to seek an anatomic instead of a clinical diagnosis on the death certificate Physicians should be taught how to approach the relatives for a necropsy in a spirit that inspires respect and confidence The approach must be sympathetic and business-like The advantage for the sake of the family should be emphasized, as well as the benefit to science and the human race They should be taught to give a simple report of the observations at necropsy to the relatives Rokitsansky's method of reconstruction of the medical history from postmortem observations would be entirely fitting

In addition, plans should be started for the education of the masses Such a campaign should include religious, social, professional and political leaders Especially should efforts be made to change the antiquated laws by an appeal to the legislative bodies

We should emphasize the value of postmortem examinations to our knowledge of medicine and the benefits derived from an enlightened medical profession. Health columns in the daily press, radio talks and special articles in the weekly and monthly journals may be tactfully and opportunely used. Efforts should be made to have an autopsy on every notable character, and the principal observations given publicity, so far as medical ethics permit. Finally, repeated attempts should be made to obtain the highly desirable cooperation of the undertaking profession.

THE PHYSIOLOGIC RÔLE OF COPPER ARTHUR LOCKE and E. R. MAIN

An analysis of the distribution of copper among the bacteria has indicated that the metal may be an essential constituent, concerned with the vital function of activating the organic molecules which take part in cellular respiration and synthesis.

VENTRAL SYMMETRIC HYPEROSTOSIS OF THE INNER TABLE OF THE CALVARIUM LEROY W. YOLTON

The complete report will be published in the ARCHIVES OF PATHOLOGY

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Oct 24, 1929

HARRISON S. MARTLAND, *Presiding*

NEPHROSIS IN MULTIPLE MYELOMA DAVID PERLA and LAWRENCE HUNTER (by invitation)

Two instances of multiple myeloma with severe nephrosis with shrinkage of the kidney were reported. A review of the literature revealed several other similar instances. A study of the pathologic changes of the kidneys in instances of multiple myeloma associated with Bence-Jones albumosuria was made. From this analysis it was concluded that the pathologic changes found in the kidney of multiple myeloma consist of three distinct conditions, no one of which is constantly present, but all three of which may be present: (1) a nephrosis specifically associated in some way with the Bence-Jones albumosuria and the myeloma, (2) arteriosclerosis of the kidney, an independent vascular disease of the kidneys, present in a milder or severer form in almost every instance of multiple myeloma occurring in the age group of 50 to 70, and (3) calcium deposits in the kidney tubules, dependent on a destruction of bone and the release of large quantities of calcium into the blood.

Clinically, the nephrosis differs from the idiopathic type in the absence of edema and in the increase in the concentration of nonprotein nitrogen in the serum and an inability to concentrate urine with a consequently low specific gravity of the urine. Anatomically, the nephrosis is severe, and the kidneys contracted. The kidneys are small and pale, with a smooth surface and marked narrowing of the cortex and medulla with replacement by a dense cellular fibrous tissue. Though there is some hyalinization of a few glomeruli, this lesion is apparently associated with a concomitant arteriosclerosis, the primary lesion being the destruction of the tubules.

DISCUSSION

PAUL KLEMPERER The most interesting fact is that in these cases of chronic nephrosis there was no edema noted. It seems then that the conception that the degenerative change in the tubules is responsible for edema, is not true. It is interesting that these cases differ so markedly, not only clinically but also histologically, from the type of nephrosis which was held to be the most characteristic type of nephrosis, lipid nephrosis. The more one studies such cases, the more one becomes convinced that the renal change is unimportant, and that the disease called

lipoid nephrosis has nothing to do with the kidney I think the cases reported by Dr Perla support such a conception

NICHOLAS ALTER What special staining methods have been used to determine the histologic nature of the degeneration?

HARRISON S MARTLAND In the first case reported, did I understand you to say that there were extraskeletal lesions in the spleen and liver?

DAVID PERLA Yes, small foci

HARRISON S MARTLAND Were they in the form of small, definite tumor formations, or just areas of myeloid metaplasia?

DAVID PERLA They generally occurred in the capillaries

HARRISON S MARTLAND I have had an idea that some forms of multiple myeloma, especially those in which the myeloblast and the erythroblast are the type cells, are closely related to panmyelosis I have seen a single physical agent, viz, undue exposure to the x-rays and radium, produce several important diseases of the blood-forming organs, such as aregenerative leukopenic anemias, regenerative leukopenic anemias of the pernicious type, myeloblastic leukemias, lymphoblastic leukemias, osteogenic sarcoma of bones, radiation osteitis and panmyelosis, in one case so extensive as to mimic multiple myeloma, the flat bones of the skull being the seat of definite tumors of myeloid origin

DAVID PERLA In reply to Dr Alter, no particular staining methods were used, we did try a great many strains recommended for the determination of the character of the protein substance in the tubules I can give you the reference to the article which mentions the staining methods

NICHOLAS ALTER It would be important to differentiate it histologically from lipoid nephrosis

DAVID PERLA It seems to me the difference is obvious In the ordinary lipoid nephrosis, you do not get the extreme contraction of the kidney There were, however, fine lipoid droplets in the intact tubules

ADENOMYOSIS OF THE URINARY BLADDER DEMONSTRATION OF CONTINUITY BETWEEN A GLANDULAR DUCT AND A BLOOD VESSEL ALFRED PLAUT

A woman, 25 years old, without any relevant previous history, had suffered from dyspareunia and dysmenorrhea since her marriage one year before On physical examination, adnexal adhesions were found The other observations were unimportant To his dismay, the surgeon at operation encountered a firm mass infiltrating the urinary bladder from behind The pathologist consulted asked whether there had been urinary symptoms at the time of menstruation After this was answered in the affirmative, he ventured a diagnosis of adenomyosis and suggested doing no radical operation, but excising only what could be taken without injury to the bladder Rapid frozen section confirmed the diagnosis The patient remained in good health

Many specimens of adenomyosis in different organs, notably in the appendix vermiformis, have suggested to the author, as well as to others, the possibility and the high probability that glandular ducts might originate from lymph vessels or blood vessels The literature contains a number of photomicrographs showing continuity between lymph spaces with low lining cells and glandular spaces with high cylindric epithelium The fact, however, that epithelial cells may appear flattened, even without distention of the gland, and that endothelial cells may become high, makes it difficult to prove endothelial origin of epithelium to a skeptic We consider ourselves fortunate, therefore, that this specimen of adenomyosis of the urinary bladder furnishes a series where a typical endometrium-like glandular duct is continuous with a blood vessel characterized by its elastic layers (Demonstration of series)

It is impossible to describe the series in a short abstract The structure in question can be followed from the typical gland through stages in which the typical gland is surrounded by thick elastic layers to further stages in which

the lining is partly high cylindric and partly flat, like typical endometrium, finally to an ordinary blood vessel. Many glandular ducts in the slides have fragments of elastic tissue under the epithelium. It is the purpose of this paper to demonstrate the series for discussion. All theoretical considerations must be deferred.

DISCUSSION

PAUL KLEMPERER I would not like to say that blood vessels and lymph vessels cannot develop glandlike structures. It is well known that one is sometimes startled by the presence of typical glandular structures lined with high endothelium in the pericardium in subacute or chronic inflammation. If Dr. Plaut thinks that some of the glandular structures in his series are definitely identical with blood vessels, it means that these glands have to be considered as of endothelial origin. In Dr. Plaut's series, one point struck me as peculiar. At the beginning of the series there was cytogenic tissue, and next to this the gland which he showed passing into a blood vessel. It seemed to me that the cytogenic tissue which we saw in the beginning of the series did not belong to this glandular structure, but to the adjacent one. I believe that there is a possibility that we are misinterpreting some apparently glandular structures when we consider them as mesodermal, that is, müllerian in origin, and not as mesenchymal, but I wonder if this is not an unusual occurrence. Or does the explanation which Dr. Plaut wishes to propose hold for the majority of the glandular structures in endometriosis?

LOUIS GROSS I would like to ask whether Dr. Plaut attempted to make a wax model or some other reconstruction of this interesting specimen. I was struck by the same difficulty as was Dr. Klemperer, and that is, at one point in the series I was able to trace the apparent changes in the glandlike structure, and then there was an abrupt change into what appeared to be a blood vessel. Could it not be possible that we were coming to the end of the gland on one side, and found a knuckle of blood vessel on the other side? A wax-model reconstruction might be able to settle this question. Did you find any smooth muscle developing in this blood vessel, or what turned out to be blood vessel?

NICHOLAS M. ALTER Endometriosis is always an embarrassing problem for the pathologists. I want to mention only some freakish cases. In one case, a young woman had hemorrhagic urination during menstruation. It could have been considered as a case of vicarious menstruation. Cystoscopic examination showed no ulceration of the bladder. When she came to the operating table, I had an opportunity to look into her abdomen as I was called for a frozen section. There was a nodule about 4 cm. in diameter over the convexity of the bladder posteriorly. Malignancy was thought of. It had to be resected with the mucosa of the bladder. In this nodule the histology of the glandular structures justified the diagnosis of so-called "endometriosis." In this particular case, the glands were traced per continuity from the nodule of the bladder wall through the adhesions to the uterus, which also showed diffuse adenomyositis. In another freak case, still more striking, a young woman had symptoms of appendicitis every month when she menstruated. Her appendix showed not only the usual microscopic picture of "endometriosis," but marked decidual changes of the stroma cells. In both these cases, the endometrial nature of these gland structures was demonstrated not only in the morphologic appearance, but also in the functional features. It would be out of place to discuss, here, whether these glands came from the uterine lining and how, or whether they differentiated to typical endometrial tissue from embryonic anlagen and came later also under the influence of ovarian action. I admit that preparations which Dr. Plaut produced with much care and labor, and which I studied but superficially, are strongly suggestive, but to me not convincing. There is no definite evidence that the glands and elastic tissue, although apparently intimately related, are of the same origin. As far as endothelial cells are concerned, metaplasia can change them to a higher type, but I would like to ask Dr. Plaut whether he found any ciliated cells.

ALFRED PLAUT In reply to Dr Gross, I hope we may make a wax model on a suitable case. I could not do it here because there was no more material.

Regarding Dr Klemperer's question as to whether I consider all endometrioses subject to this explanation—certainly not. O Frankl and his associates have proved the direct origin from the endometrium of certain endometrioses beyond any doubt. We have all seen the origin from the peritoneum beyond any doubt, and I hope that we will have a third origin of endometriosis, which I would like to call the interstitial. The relative frequency of these different origins has to be established. There is no reason why an unknown hormonal stimulus, probably ovarian, should not act on different elements in the same way. There is no reason why it should not stimulate the peritoneum and the endometrium and the mesenchymal cells, as well.

About the muscle tissue in the blood vessel walls, I would have to go over the slides again before I could answer that question.

The so-called glands in pericarditis I would not put in a direct parallel with the glands shown here, in my mind, they are vascular spaces with high endothelium. I do not believe that this comparison holds until we have seen the functional proof that these glands lined by high cells in the pericardium are really functioning secreting glands.

DR ALTER said in one of his cases that bladder mucosa had to be resected. Adenomyosis invading the wall of the rectum or bladder practically always leaves the mucosa intact.

Reference to anlagen for an explanation, in my opinion, means we have no explanation. For instance, when the vaginal wall is completely full of glandular structures, and the trouble has developed at the age of 55, I do not see how a congenital anlage can have anything to do with it. It is the same with a diffuse endometriosis in the appendix and other organs.

I expected the series would be convincing to everybody, but I would like to ask how to explain the elastic lamellae around the gland. Even if we did not have the continuity with this blood vessel, how would one explain that a simple endometrium-like gland is surrounded by heavy layers of elastic tissue? I have seen many thousands of slides from adenomyosis, and so far I have not seen such heavy elastic layers. I am going to stain all slides of adenomyosis with Weigert's, and report to you next year or in two years what I find.

ACUTE HEMOLYTIC ANEMIA. THREE ADDITIONAL CASES WITH A REVIEW OF THE LITERATURE. MAX LEDERER

In 1925, in the *American Journal of Medical Sciences* (170:500, 1925), the author published a description of three cases of an undescribed form of acute hemolytic anemia. These cases presented a clinical picture of anemia which developed within a few days and progressed at an alarming rate. In the present communication, a study of three additional cases observed by the author is reported, with a resume of the literature including three others mentioned by various authors. All six cases presented similar clinical and hematologic pictures, with certain variations. The age incidence was from 6 months to 35 years. Five were in males and one in a female. The history of onset in three cases was three days, in two, six days, and in one, two days. The onset in all six was characterized by the rapid development of pallor, icterus, weakness and rise of temperature. In four there was vomiting, in one diarrhea, in one backache, in one headache and in two hemoglobinuria. On physical examination, six showed pallor and icterus and five fever, while in four there was noted splenic enlargement, and in three hepatic enlargement. The classic evidences of hemolysis were demonstrable in all. The blood showed in all cases a severe anemia, the red cell count falling in one case to 760,000 per cubic millimeter, the stained preparation in all cases showed the presence of varying numbers of megaloblasts and erythroblasts and myeloblasts. All the patients promptly recovered after a transfusion of unmodified blood, the nucleated red cells disappearing within twenty-four hours and the hemoglobin and red cell count increasing rapidly, in some instances

up to more than three times. Restudy of the patients several years after recovery showed no sequelae in any instance.

DISCUSSION

CHARLES NORRIS I would like to ask if a seasonal occurrence has been observed, and if the cases were all in Brooklyn, and if they were, did they all come from the same district?

ELI MOSCHCOWITZ I think Dr Lederer is lucky to have seen all these cases. I have kept my eyes open for other cases, but have not had the occasion to see another since my last report. There is no doubt that the case which I reported seemed like those of Dr Lederer, except that in his cases the patients all recovered. It is true that the examinations of the blood in my case were not as carefully done as in Dr Lederer's cases. My case occurred in a child with a rapidly increasing anemia, which was accompanied by a high color index, as in Dr Lederer's cases a transfusion was done, but the patient did not recover. At autopsy, I found hyaline thrombi in the peripheral arterioles and in the capillaries. Obviously, the six cases which Dr Lederer reports represent nothing more than a clinical syndrome thus far. In order to complete his study and to make this a definite disease, a precise pathologic study is still necessary.

FREDERICK H. DIETRICH Have all these cases the same racial background?

LOUIS GROSS The striking increase in red blood cells within forty-eight hours makes one wonder whether increased blood concentration at this period may not be at least a factor. Did you make any studies of the blood volume during this remarkably sudden increase in red blood cells?

ALFRED PLAUT I want to ask two purely technical questions. I would like to ask how a hemoglobin of 14 is read. With the Sahli instrument, I am unable to make a reading below 30. My second pedantic technical point is why does everybody, including Dr Lederer, report the number of nucleated red cells in relation to the leukocytes. In my opinion, they have nothing to do with each other, and I always give the number of nucleated cells in relation to the number of red cells, which in my opinion is the more logical way. I would like to know whether any such case is on record which has become chronic. I had the opportunity of seeing a patient who for twenty years has had a hemoglobin around 40, and 5 per cent nucleated red cells, without being very sick.

H. S. MARTLAND Could the chronic, more or less benign cases be confused with von Jaksch's anemia or the erythroblastic anemias of infancy? Are the acute cases essentially cases of hemolytic anemia due to increased activity of the reticulo-endothelial system, or have you formed any opinion as to their etiology?

MAX LEDERER Regarding Dr Martland's question, in 1925 Dr Klemperer, in a personal communication, suggested as an explanation that the exciting agent of the disease exercised a selective action on the reticulo-endothelial system as a whole, affecting its productive, as well as its destructive, function, that the erythroblastosis is accounted for by the stimulation of the productive function and the hemolytic anemia by the stimulation of the destructive components and that the destruction continues at a greater rate than the production.

H. S. MARTLAND Were there many immature leukocytes in the circulating blood?

MAX LEDERER Regarding the leukocytes, the myeloid tissues are stimulated causing an increased production of leukocytes with the appearance of small numbers of immature forms. The high degree of leukocytosis is probably due to this excessive production, and since the reticulo-endothelial system does not concern itself with the destruction of leukocytes, they heap up in great numbers.

As far as seasonal incidence is concerned, the cases occurred at all times of the year. They were not confined to Brooklyn. One case occurred in the mountains after a vacation to increase hemoglobin. There were two cases reported in Denmark, one in France and one in Missouri.

As far as race is concerned, two cases were in Danes and two cases, which are going to be reported by Dr Lazarus, were in negroes

In regard to blood volume, we have not done any studies on blood volume. The general appearance of the patients following transfusion, and their remarkable improvement showed a profound increase in the number of blood cells. The hemolysis due to the destruction of red cells was manifested in the tremendous hemoglobinuria.

I agree with Dr Plaut regarding the reading of a hemoglobin of 14, that is more or less arbitrary. We use the Dare hemoglobinometer exclusively, and our Dare is thoroughly checked by the Newcomer, so we are certain that the readings on the Dare are close to those obtained on the Newcomer. The only reason for reporting erythroblasts in terms of the number of leukocytes per hundred cubic centimeters is because erythroblasts are counted at the same time the differential count is done, and it is a habit we have fallen into. I do not suppose anybody has had the courage to report them in absolute numbers, as most of us do not report the differential white cells in absolute numbers. The studies had to be done quickly, and the blood specimens obtained were examined quickly, so we feel that the figures, as we gave them for practical purposes, emphasized the diagnostic point as well as would an absolute count.

BALANTIDIUM COLI ENTERITIS. REPORT OF A CASE OBSERVED IN NEW YORK CITY. HERBERT LAMPERT (by invitation)

This case of balantidial colitis occurred in a 60 year old Porto Rican woman who died from pneumonia. The lesions, which were found at autopsy, were limited to the entire length of the colon. The ulcerations resembled those of amebic dysentery. It was noted that the more recent ulcerations were located at the proximal portion of the colon, while the more chronic lesions were situated more distally.

In attempting to study the manner in which the balantidia invaded the mucosa, serial sections were cut and examined, of what was apparently normal mucosa. Sections were shown in which the balantidia were seen within the crypts of the colon, which were distended with an exudate of polymorphonuclear leukocytes and debris. Other sections showed the gradual erosion of the mucosal gland with extension along the lymphatics to other portions of the colon. All the ulcerations showed secondary bacterial invasion. Many of the balantidia were found within large blood vessels. In spite of the latter observation, there were no lesions found in either the liver or the lungs, although such observations have been reported by other investigators.

DISCUSSION

PAUL KLEMPERER. In view of the increasing Porto Rican population, I think it is important to emphasize that we can expect to find such and similar cases.

FIBROSARCOMA OF THE PLEURA IN ITS RELATION TO ENDOTHELIOMA. G. V. RABIN (by invitation)

The paper refers to the diffuse type of pleural tumors which completely ensheath the lung. There have been about eighty cases reported under various headings as carcinoma, endothelioma and sarcoma. The endotheliomas are considered as arising from either the serous lining cells or the cells of the subpleural lymphatics. In the latter cases, however, the growths appear rather to be extensions to the pleural lymphatics from primary pulmonary tumors.

A case was presented of a diffuse pleural neoplasm which showed both epithelial and mesenchymal characteristics. The patient, a girl, 18 years of age, was admitted with a history of pain in the left side of the chest for eighteen months. On physical examination, the left side of the chest was found to bulge forward markedly. The percussion note was flat. The roentgenogram showed a diffuse shadow over the entire left side of the chest with marked displacement of the heart to the right. On pleural puncture, the needle met with great

resistance No fluid was withdrawn, but a particle of tissue removed with the needle showed histologically a picture that resembled a spindle cell sarcoma

The patient died shortly thereafter At autopsy, the left lung was found collapsed and completely ensheathed by a thick nodular neoplasm which infiltrated the chest wall Histologic examination showed the tumor to be made up of cells, distinctly epithelial, with large pale nuclei containing nucleoli and a sharp nuclear membrane The cytoplasm was abundant There were many giant cells There were, however, intercellular fibers which stained black with Bielschowsky, blue with Mallory fuchsin aniline blue, brown with the phosphotungstic hematoxylin and red with the van Gieson stain These fibers were delicate and completely surrounded each cell in most portions of the specimen

Records of three, similar types of pleural tumors were discovered in a study of the literature of sarcoma of the pleura In each case, the cells presented typically epithelial characteristics In order to explain this histologic picture, the characteristics of the mesothelial cell, the cells lining the pleura, were discussed Genetically, they are derived from the celomic epithelium, which is closely related to the mesenchyme Under experimental conditions, their fibroblastic potentialities, indicated from their embryologic origin, have been proved, both in tissue cultures and in inflammatory reaction of the pleura and peritoneum Since the mesothelial cells that line the pleural cavity are possessed of both epithelial and fibroblastic potentialities, it is concluded that the entire group of diffuse pleural neoplasms has a common origin in the mesothelium and should be considered under the one single heading of mesothelioma

DISCUSSION

ALFRED PLAUT I fully agree with Dr Rabin I would like to know whether intercellular bridges have been sought for They are found frequently, if one looks for them, in structures arising from the peritoneum As some of you will remember, several years ago I had the opportunity of reporting on peritoneal cysts here The observation of the epithelial character of the lining cells of the peritoneum is a matter of daily routine to the man who does gynecologic pathologic investigation In every tubal gestation I find high peritoneal cells In every fifth normal tube, I find typical squamous epithelium in the serosa In the last meeting of the German Pathological Society, Hamdi reported epithelial tumors of the pericardium He called them celothelioma, which is better than mesothelioma, because the term "meso-" is used for many different things

A M SALA The title of Dr Rabin's paper as given in the program led me to bring up this specimen of what I have tentatively diagnosed as fibrosarcoma It was removed at operation just a few days ago from a woman's right pleural cavity, where it seemed to spring from the diaphragmatic pleura It weighs 1,675 Gm Because this is an entirely different tumor from the one considered by Dr Rabin, I shall make it the subject of a detailed presentation before the society in the near future

C B RABIN (closing the discussion) I am glad to see that specimen It belongs to the other type, not the diffuse type of tumors, and it is only the diffuse type that I am discussing The latter are the ones which I believe should not be called fibrosarcoma, but one should realize their point of origin Sarcomas similar to the one of Dr Sala were collected and described by Schneider They form an interesting group However, they have no relationship to the type under discussion They arise from the subpleural connective tissue

In reply to Dr Plaut's question about intercellular bridges, we saw none

STUDIES IN THE CHEMISTRY AND CYTOLOGY OF SPINAL FLUID AFTER THE INJECTION OF PROCAINE HYDROCHLORIDE FOR SPINAL ANESTHESIA ALFRED H IASON and MORRIS STEINER (by invitation)

In a great majority of cases, it has been shown that spinal anesthesia is less toxic and produces less ill after-effects than general anesthesia However, cases have been cited by Munchmeyer, Madden, Gabbett, Berand, Hatcher and Eggleston

in which fatalities resulted following the use of this type of anesthesia. In addition, many cases manifested such untoward results as headache, retching, vomiting and paresthesias of the leg. It was thought that if some of these sequelae were due to toxic and irritating actions of the medicament employed, some changes in the spinal fluid must have resulted. It was with this in mind that the following investigation was undertaken.

The spinal fluid of thirty-one patients was examined before and twelve hours after the injection of procaine hydrochloride into the canal. The cytology and chemistry, which included the nitric acid ring test for albumin, the Noguchi test for globulin, Fehling's test for reducing substance, the colloidal gold reaction and finally a quantitative determination of sugar by the Folin-Wu method, were studied.

Of the thirty-one spinal fluids, only fourteen permitted accurate cytologic studies, all the others contained from few to many red blood cells, which were considered as due to trauma incidental to the lumbar tap. Of these 14, 11 showed a definite pleocytosis varying from 800 cells, all of the polymorphonuclear variety, to 20 cells, all lymphocytes. Two showed a slight pleocytosis—12 cells, all lymphocytes, one, a normal count—5 cells, all lymphocytes.

In twenty of the thirty-one cases, the quantitative determinations of sugar were studied. In all twenty cases there was an increase in the postoperative specimens varying from 7 to 135.2 per cent. In but three cases could the increase be considered within normal limits, being less than 10 per cent. The average rise calculated on the basis of percentage increase for each case was 37.3 per cent. Just what the significance of this increase in sugar is, cannot be stated. Further studies are being made in which simultaneous blood and spinal fluid sugar determinations are being done, before and after the injection of procaine hydrochloride, in order to observe whether or not any relationship exists between the sugar content of the blood and that of the spinal fluid under these conditions.

The addition of procaine hydrochloride to spinal fluid *in vitro* does not cause any increase in the reducing substance.

The albumin was not increased nor was globulin present in any of the cases. The colloidal gold was not reduced in any case, which indicates that the protein content of the spinal fluid was not altered after the injection of procaine hydrochloride for spinal anesthesia.

DISCUSSION

ALFRED H. IASON. In selecting cases, we were careful to use a variety, *i. e.*, carcinoma of breast, appendicitis, hernia and fibromyomata uteri. The age of the patients varied from 11 to 69 years. There were nine males and twenty-two females. In the oldest patient, a woman of 69, with an incarcerated hernia, the blood pressure dropped from 100 to 80, systolic, and 80 to 60, diastolic. The largest fall in systolic blood pressure was 74, and that in diastolic pressure was 42, with 10 as the lowest fall. We watched the patients for postoperative complications. Seventy-five per cent of them had to be catheterized for the first three days, six patients vomited for one day, three vomited or retched at the time of operation, two complained of pain in the right leg for two days, one complained of headache and dizziness. We also noted that in subsequent lumbar taps the rate of flow was moderately increased in 30 per cent of the cases. In children under 14 years of age, and in adults in whom the operative procedure was limited to the lower part of the abdomen, I usually found that from 75 to 125 mg, instead of a whole ampule of 200 mg, was sufficient. I also observed that when giving less than the full ampule of procaine hydrochloride a complete anesthesia was late in appearing, but there was an absence in a large degree of such operative sequelae as vomiting, urinary retention and vertigo. With a smaller amount of anesthesia, there followed an elimination of postoperative sequelae as mentioned. In a series of about a thousand cases, only one case of postoperative pneumonia occurred, which probably had no relation to the anesthesia.

FREDERIC FELDMAN (by invitation). Did you use ephedrine?

ALFRED H. IASON. We used it routinely, in children using half an ampule. We also used procaine hydrochloride without the injection of epinephrine hydro-

chloride subcutaneously to anesthetize the skin before inserting the needle into the spinal canal. I always punctured the third interspace, whether in adults or children. I reported on one adult on whom I did a radical mastectomy for carcinoma of the breast under spinal anesthesia in whom I utilized the third lumbar interspace, and when the operation was finished, I had anesthesia as far cephalad as the mastoid bone.

FREDERIC FEIDMAN Do you think the rise in sugar could be due to the ephedrine?

PAUL KLEMPERER There are a few cases on record in which after spinal anesthesia an aseptic meningitis occurred, in all these cases the patients recovered.

ALFRED H. IASON At the Jewish Hospital, we have not had any mortality from spinal anesthesia. In addition, I might add that a mild cardiac condition is not a contraindication to spinal anesthesia.

DIVERTICULA OF THE COLON ROBERT P. WALLACE

Diverticula of the colon have long been noted, but it was not until 1849 that Cruveilhier first described them in some detail. Diverticulitis was first recorded and the name added to the condition by Habershorn in 1857. It was not till 1898 that diverticula were recognized as being of much importance, when Glazier pointed this out and stressed the frequency with which they are present. The first really exhaustive paper appeared in 1904 by Beer, and three years later Moynihan's classic paper gave a differentiation from cancer and stressed its surgical importance.

Later years, with the increased frequency and accuracy of diagnosis by means of the roentgenogram, it was found that diverticula were the basis for many indefinite "colon complaints" and that the complications requiring surgical intervention were comparatively few. Chief among the present day investigators are Robertson, Case, Mailer, Patterson, Spriggs and Marxer.

Statistics from the Mayo Clinic showed records of 1,918 cases of diverticulosis. At autopsy, Robertson found that 5 per cent of the people past 40 years of age had diverticula of the colon. Also at autopsy, Mailer found 7 per cent of the adults had colonic diverticula. These observations fairly well approximate the results of roentgen examination, for in 26,700 cases of gastro-intestinal disease 5.9 per cent were associated with diverticula. On the other hand, Spriggs and Marxer in England found in 1,000 consecutive cases 10 per cent with colonic and 1 per cent with small intestinal diverticula. They also state that half the demonstrated diverticula gave symptoms after observation over a number of years and the other half were silent. These are the highest figures that I have been able to find.

Diverticula formerly were described as being of congenital and acquired origin. The congenital type consisted of all coatings of the intestine, while the acquired type represented herniations of the mucosa and submucosa through the muscle wall. This classification is still mentioned now, but it is the trend of thought that most of the colonic diverticula are acquired, and it is doubted whether or not congenital pocketings occur in this location.

Diverticula of the duodenum, on the other hand, are probably for the most part congenital and differ materially from the others in that they contain the whole intestinal coating, have wide openings, are shallow and frequently contain gastric mucosa or pancreatic tissue at their tips. This belief was given further credence when Dr. Thyng demonstrated such diverticula of the duodenum in the embryo.

The prediverticular state, that is, before sacculization has occurred, was described in 1925 by Marxer. His description was based on x-ray evidence, and when subsequent films were made several years later actual sacculization was demonstrated in such areas. Surgical specimens of such a stage, when examined microscopically, reveal that this portion of the intestine is inflamed and there is a thinning out of the musculature. This was observed by Glazier, Patterson and Wilson.

In the colon, diverticula occur in any portion of the circumference of the intestine, but most usually on the antimesenteric border where the blood vessels and lymphatics enter. In the small intestine, however, they occur between the layers of the mesentery. In the large intestine, the sacs are usually numerous and small, and have small openings, while in the small intestine the sacs become much larger.

Pathologic Changes in Diverticula—In serial x-ray pictures, it has been shown that diverticula contract, as peristaltic waves progress through the gut, in an effort to expel the contents. However, as the sac becomes larger, the muscle fibers disappear, the contents stagnate and become hardened. This stercolith by pressure and irritation excites inflammation. This starts first at the neck and opening of the sac and spreads into the sac and onto the wall of the colon. This area is not often the site of ulceration, but fibroblasts invade it, and scar tissue is formed. As this contracts, the opening is widened, the depth of the sac is diminished and the contents are gradually evacuated. This is another example of the remarkable reparative process that occurs in the body following injury.

DISCUSSION

CHARLES T. OLCOTT. There were twenty or thirty diverticula in the first portion of the jejunum in the patient, a specimen of which I brought to exhibit. The patient was a man of 71 who died of a perforated gastric ulcer. He also had a diverticulum of the duodenum. The diverticula were an accidental observation at autopsy.

BORIS KWARTIN. I should like to ask if all these cases were postmortem or operative cases. In one case of a neurotic young man about 21 years old who complained of gastro-intestinal symptoms of a vague character, a series of x-ray pictures was taken, and a permanent defect was found in the postpyloric region, on account of the x-ray evidence, rather than the symptoms, an operation was performed. When I received the specimen, I could not demonstrate an ulcer, but I did not find a little diverticulum, 2 by 2.5 cm. All the coats were completely intact. It was covered by mucosa and there were no signs of inflammation or other pathologic change.

PAUL KLEMPERER. These juxtapyloric diverticula are not so rare, I find them rather frequently. An interesting case was that of a diverticulum near the papilla of Vater, pressing on the common duct. In this case, the main symptom of the patient was jaundice, for which an operation had been performed and it was apparently due to the pressure of the diverticulum on the common duct.

ROBERT P. WALLACE. These were all observed at autopsies, and they have become so frequent that they are not a rarity any more.

Book Reviews

THE LIFE OF HERMANN M. BIGGS, M.D., D.Sc., LL.D., PHYSICIAN AND STATESMAN OF THE PUBLIC HEALTH By C-E A. WINSLOW, DR. P. H., Professor of Public Health, Yale School of Medicine, Member, Health Committee, League of Nations, Geneva, Member, Public Health Council, State of Connecticut, Past President, Society of American Bacteriologists and American Public Health Association. Cloth. Price, \$5, net. Pp. 432, with illustrations. Philadelphia: Lea & Febiger.

Here is an interesting biography of a physician who began his medical career as a pathologist and became one of the great leaders of the world in public health. Hermann Michael Biggs (1859-1923) was graduated from Bellevue Medical College in 1883 and served as intern in Bellevue Hospital. Many years later he commented on this period as follows: "It seems strange often in looking back after half a life-time, over the passage of many years, what apparently insignificant incidents have determined largely the course of one's life. How clearly now I recall the incident which first directed my thoughts to bacteriology and tuberculosis. I was in my last year of medical school. Our beloved friend, Dr. Welch, was Professor of Pathology at Bellevue and was conducting a private class in normal and pathological histology. I was a member of one of those classes, just after the publication of Koch's classical work on the Etiology of Tuberculosis. In his most lucid and fascinating manner he told us of this great work and its significance to the future development of medicine. He showed us methods of staining sputum and demonstrated tubercle bacilli. I can see now quite clearly the steam rising from the dish of Carbol-fuchsin in the sand-bath containing sputum, while he talked. This served as my first inspiration."

The book is rich in choice illuminating glimpses like this. It is worthy of note that Biggs' first teacher in pathology now writes with comprehensive grasp the introduction to this biography of his pupil. When Biggs returned from Germany in 1885 he was appointed one of the instructors in the Carnegie Laboratory, then just opened, and gave instruction in bacteriology. He also came early into close relations with that other great pioneer American pathologist, T. Mitchell Prudden, whom he spoke of as his "silent but influential partner" and who played a highly significant part in the development, in intimate association with Biggs, of the work of the Health Department in New York City. One meets these two pathologists again and again in the book. Biggs also practiced medicine and was a trusted physician and excellent consultant. He was successively teacher of pathology, of therapeutics and of medicine, and during his earlier professional years he published papers on pathologic subjects. He was president of the New York Pathological Society in 1891. These facts are cited not merely to show that Biggs entered on his great life-work by the gateway of pathology, but also to make it clear that his biographer incidentally throws vivid sidelights on the early history of pathology in this country.

Shortly after Biggs became connected with the Carnegie Laboratory he was sent to Plymouth, Pa., to study the famous outbreak there of typhoid fever, but it was not until 1887 that he began to do work for the New York City Health Department. The occasion was the danger of the introduction of cholera, and he then suggested the advisability of establishing in the department a division of bacteriology and disinfection. This is the beginning of his work in public health on which his permanent fame so securely rests. The achievements credited to him in this field are monumental. His four major contributions to public health administration while in the service of the city of New York are listed as follows by his biographer: Establishment of the first municipal diagnostic and research public health laboratory, the administrative control of diphtheria

and the administrative introduction of diphtheria antitoxin, the administrative control of tuberculosis, and the program for the protection of child health Biggs severed his connection of more than twenty-six years with the city health department at the beginning of 1914 to become State Health Commissioner, finally accepting the position after much persuasion. Previously he had been chairman of a commission that had prepared a new, recently enacted state public health law, which included important reforms. In the conduct of the state office "he demonstrated concrete administrative procedures which have formed the models for all subsequent progress in the difficult art of community health organization." The circumstantial story of the life of this man who modernized public health administration in accord with the newer knowledge of infection and in other fields as told in this book is of unusual interest. The rich materials are handled with great skill and competence. The style is clear and fluent. Biggs is fortunate in his biographer. Incidentally, there is traced at the same time the development of modern public health administration as necessary to provide the proper background for understanding the significance of Biggs' work. Many figures—scientists, teachers, administrators, politicians—move across the pages and help to tell how a quiet, rather silent man, with a frail constitution, rose to "a position almost unique in public confidence and influence in matters concerned with health and control of disease." The illustrations, mostly portraits, add to the interest. The publisher has done his part well. The book is an important and attractive addition to the biographic literature and is an outstanding medical biography.

THE FEMALE SEX HORMONE. By ROBERT T. FRANK, M.D., Gynecologist to Mt Sinai Hospital. Price, \$5.50. Pp 324, with 86 illustrations and 36 graphs. Springfield, Ill. Charles C. Thomas, 1929.

This elaborate monograph concerning the female sex hormone, in the field of which the author has done so much work of fundamental importance, is divided into two main parts. The first part deals first with anatomic and physiologic matters of basic significance and then with the results of the investigations of the female sex hormone, its actions, sources and chemical nature. The presentation is minute and detailed, so much so as to be almost confusing at times, but it gives a reliable and complete summary of the literature in question. For this reason the book will be a helpful guide to sources for other workers. At the end of part I is a list of 491 complete references. The second part presents the results of clinical investigations by the author on the basis of "the female sex hormone blood test." The technic of the test and the results of its application under various conditions, the physiologic actions of the hormone on women and the treatment for functional diseases of the female reproductive organs are described in detail. At the end is a further list of references, numbers 491A-518, and as the previous list is referred to frequently in this part, it seems that the two lists of references might have been consolidated with advantage into one list at the end. In view of the great many details, frequently repetitious, in both parts I and II, it is of great value that the last chapter gives a clear and connected statement in summary and review. There is complete both subject and author index. The book is an earnest, able and successful effort to picture the present state of our knowledge of the female sex hormone. The rapid progress is impressive and the outlook promising.

GREEK MEDICINE, BEING EXTRACTS ILLUSTRATIVE OF MEDICAL WRITERS FROM HIPPOCRATES TO GALEN. Translated and annotated by ARTHUR J. BROCK, M.D. (Edinburgh), translator and commentator of Galen. Price, \$1.75. Pp 256. New York. E. P. Dutton & Company.

The translator writes an instructive and interesting introduction on Greek medicine and its development, with Hippocrates, his teachings and Galen as the main topics. One commonly speaks of Hippocrates and Galen as practically

contemporaneous, but they are separated by six hundred years, and Galen always includes Hippocrates among "the Ancients." Many persons will be surprised to learn how much is known about Galen himself, mainly from autobiographic glimpses in his medical writings. In commenting on certain ancient theories, Dr Brock makes the startling statement (page 17) that "if the doctrine of Erasistratus shows certain parallels with Osteopathy, that of Asclepiades reminds us of yet another modern medical system, also of American origin, namely, the so-called 'Electronic Reaction of Abrams'." As Asclepiades employed the then new atomic theory in explaining vital processes, similarly Dr Albert Abrams of San Francisco (1863-1924) did with the modern theory of electrons." Dr Brock's knowledge of Abrams' claims and their nature is sadly defective. The main part of the book is made up of translations with introductory annotations of extracts from Hippocrates and Galen. There are translations also of short extracts from Plato, Aristotle, Rufus of Ephesus, Diodorus and Aetius. All the extracts included, except those from Aristotle, have been translated by Dr Brock directly from the Greek. There is a helpful index. The book is a capital introduction to Greek medicine. The first Hippocratic aphorism, as translated in this book, follows: "Life is short, the Art long, occasion sudden, experience fallible, and judgment difficult. Not only must the physician show himself prepared to do what is needed, he must make the patient, the attendants, and the surrounding circumstances cooperate with him."

KLINISCHE LABORATORIUMSTECHNIK HERAUSGEGEBEN VON PROF. DR. THEODOR BRUGSCH und PROF. DR. ALFRED SCHITTENHEIM. Zweite, Vollständig neu bearbeitete Auflage der "Technik der Speziellen Klinischen Untersuchungsmethoden." Volume 4. Paper Price, 50 marks. Pp. 2101-2840, with 328 illustrations and 8 colored plates. Berlin and Vienna. Urban & Schwarzenberg, 1929.

This volume contains technical and critical descriptions of the biologic diagnosis of pregnancy by H. Runge, skin function tests by Schwenkenbecher and Moog, diagnosis of the nervous system by H. Lewy, psychologic methods, with especial regard to vocational tests, by A. Moll, psychiatric methods by Birnbaum, esophagoscopy by W. Wolff, gastroscopy by H. Elsner, proctosigmoidoscopy by H. Strauss, thoracoscopy by Jakobalus, tracheobronchoscopy and laryngoscopy by W. Fruhwald, rhinoscopy by J. Schmeier, examination of the acoustic apparatus and of the labyrinth by O. Benesi, examination of the accessory nasal cavities by J. Fischer, cystoscopy by Rumpel and ophthalmoscopy by W. Meisner.

The editors make the comment that all these methods have developed in such close contact with internal medicine that they have become part of it. They admit that the title of the work has become too narrow for its contents and would now prefer to call it "Working Methods of Scientific Medicine." It seems, however, like a wasteful duplication of effort to attempt to bring into one book so many methods which require special technical training and which are better dealt with in monographs. No conscientious internist will attempt to perform gastroscopy without special study and technical training, and some will not have it done even by experts. Superfluous as many chapters seem they are nevertheless interesting to read and may increase the general information of the specialist. An abundance of references to German literature and an index of 47 pages are of course valuable assets of the work.

Books Received

THE ADRENALS, THEIR PHYSIOLOGY, PATHOLOGY AND DISEASES By Max A Goldzieher, M D, former Professor of Pathology, University of Budapest, Director of Laboratories, United Israel Zion Hospital, Brooklyn, N Y Price, \$7 50 Pp 436 New York The Macmillan Company, 1929

THE MEDICAL MUSEUM, MODERN DEVELOPMENTS, ORGANIZATION AND TECHNICAL METHODS BASED ON A NEW SYSTEM OF VISUAL TEACHING By S H Daukes, O B E, M D, D P H, D T M & H, Director of the Wellcome Museum of Medical Sciences affiliated to the Bureau of Scientific Research Pp 172, with 44 illustrations London The Wellcome Foundation Ltd, 1929

METHODS AND PROBLEMS OF MEDICAL EDUCATION Fifteenth Series Pp 76 New York Rockefeller Foundation, 1929

This number contains a complete description of the Albany Medical College, Union University, Albany, N Y

INSECTS, TICKS, MITES AND VENOMOUS ANIMALS OF MEDICAL AND VETERINARY IMPORTANCE By Walter Scott Patton, M B, Ch B (Edin), F E S, Dutton Memorial Professor of Entomology, Liverpool University and Liverpool School of Tropical Medicine, and Alwen M Evans, D Sc, Lecturer on Entomology, Liverpool School of Tropical Medicine Part 1 Medical Pp 785, with 374 illustrations, 60 color plates, 3 maps and a large illustrated revision sheet Price, 20 shillings, postpaid Liverpool School of Tropical Medicine, 1929

THE HEALTH OF WORKERS IN DUSTY TRADES II EXPOSURE TO SILICEOUS DUST (GRANITE INDUSTRY) By A E Russell, Past Assistant Surgeon, R H Britten, Associate Statistician, L R Thompson, Surgeon, J J Bloomfield, Assistant Chemical Engineer, U S Public Health Service (with sections on autopsy material by Dr L U Gardner, and on silica by Prof A Knopf) United States Public Health Service Bulletin 187, July, 1929 Price, \$1 15 Pp 206 Washington, D C U S Government Printing Office, 1929

CONTRIBUTIONS FROM THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA, 1922-1929 Philadelphia Zoological Society, 1929

BACTERIOLOGY, ESPECIALLY DETERMINATIVE BACTERIOLOGY By Prof Dr K B Lehmann of Wurzburg and Prof Dr R O Neumann of Hamburg Seventh edition Volume 1 A, parts A and B Technique and General Determinative Bacteriology Translated by Dr Robert S Breed, Chief in Research, New York Agricultural Experiment Station, Geneva, N Y Pp 103, with 5 colored plates New York G E Stechert & Company (Alfred Hafner), 1930

ARCHIVES OF PATHOLOGY

VOLUME 9

JANUARY, 1930—PART II

NUMBER 1

The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients

WILLIAM F PETERSEN, M D

AND

SAMUEL A LEVINSON, M D

Department of Pathology, University of Illinois College of Medicine, and
the Research Laboratory, Municipal Tuberculosis Sanitarium
CHICAGO

We are under obligation to the following collaborators

ALBERT BACHEM, Ph D, Professor of Biophysics, University of Illinois (measurements of muscular irritability and of electrical conductivity of skin)

ADOLPH HARTUNG, M D, Professor of Roentgenology, University of Illinois (examination of all roentgenograms)

MICHAEL GOLDENBURG, M D, Surgeon, Illinois Charitable Eye and Ear Infirmary (examination and reference of all patients with glaucoma)

LINDON SEED, M D, Associate, Department of Surgery, University of Illinois (examination and reference of all patients with exophthalmos)

In the technical and statistical work we gratefully acknowledge the assistance of the late Sergius Arquin, M D, George Milles, M D, Knute Reuterskjold, M D, William Boikan, M D, Louis Richberg, M D, Louis Parmacek, M D, and Miss Mildred Rosenberg

Mrs Helen Kahn, Serologist, Research and Educational Hospital, carried out the Wassermann Tests, R G McFate, M S, Chemist, Research and Educational Hospital, the cholesterol determinations

Financial support was accorded us from the funds of the Graduate School of the University of Illinois

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I GENERAL CORRELATIONS IN ONE HUNDRED SO-CALLED NORMAL MEN*

The studies in which during the past five years, one of us (W F P) has been interested had their inception in the problems of nonspecific resistance to disease. Closely associated has been a consideration both of allergy and of autonomic derangement, during the course of which individuals react in an abnormal manner to a nonspecific stimulus.

The clinical picture of disease is obviously the reaction of the individual organ or the organism as a whole to an insult. Normally, the insult provokes stimulation, made manifest in various ways, but cellular inhibition, fatigue, paralysis and death may all play a part simultaneously in the sum total of this clinical picture. Not only does the insult vary qualitatively as it may quantitatively, but the individual response will be modified because of inherent differences in the inherited germ plasm, because of differences in the relative activity or inactivity of the glands of internal secretion, because of diet, age, fatigue, previous experience (sensitization or immunity), preexisting or concomitant disease, psychic states, climate, temperature, etc.

It is a subject that does not lend itself readily to study because the degrees of reactivity of the different tissues of the body which we commonly use for examination (skin, nervous tissues, mesenchyme [bone-marrow, leukocytes, endothelium, etc.]) are not necessarily coordinate. Certainly, the reactivity of the epithelium may not correspond with that of the smooth musculature of the blood vessels, and the smooth musculature of the blood vessels may give no index of the status of the capillary endothelium. Recent investigations of the autonomic responses of the body have made this clear.

In its broader aspects, such a study deals with individual constitutional reactivity. But we have felt that in seeking to define constitution in terms of measurable biologic reactions rather than in developmental attributes, some progress might be achieved. The clinician speaks of "lowered resistance" or "good resistance." Generally that is an estimate based on the appearance of the patient, the color and the texture of the skin, the muscular development, the posture and the tonus, the appearance of the fat depots and of the mucous membranes and the mental attitude—the many subtle differences in the physical appearance of the patient. In making his general estimate, the physician usually fuses both constitutional factors and the factors that are the result of environmental forces (condition).

* From the Department of Pathology of the University of Illinois College of Medicine

To Eppinger and Hess¹ we owe the introduction of one of the first of the modern methods useful in the estimation of individual reactivity, namely, the injection of epinephrine hydrochloride. Eppinger and Hess classified their patients as sympathicotonic or vagotonic. Clinical experience, however, has clearly demonstrated that this sharp division is not tenable, that there are many gradients. In addition, it is known that the relative reactivity of the smooth musculature of the blood vessels is by no means a criterion of the relative reactivity of other tissues.

Such studies of the reactivity of the patient are by no means of purely theoretical interest. It is true that the subject of inflammation per se, having progressed through cycles of interpretation from the periods purely speculative to the period of intensive objective research, from which it is just emerging, seems, perhaps because of the very mass of accumulated information, now in danger of being submerged in metaphysical abstractions or a one-sided insistence on relatively unimportant detail. This is unfortunate, because inflammation should be a subject for clinical, never philosophic, study.

Partly, the difficulty is to be sought in the fact that the purely histologic concept of pathology is no longer adequate to the pace of the correlated sciences. Pathology is stepping from cellular to molecular changes and histology must make ever greater use of chemical and physical tools. Partly, the reason is to be sought in the definite realization of an all-embracing interrelation and integration of cell and organ functions that make up the totality of the person. While, therefore, the interests of investigators must center on ever smaller objects as they approach molecular pathology, these interests must, at the same time, become wider as they include constitutional pathology, the study of the functional reactions of the entire organism. It is no longer possible to expect a satisfying solution of problems unless the range of the inquiry is so extended.

Schade² led the way in bringing together much of the pioneer work that underlies molecular pathology. The entire range of subjects grouped together as pathologic physiology forms the real background. Particularly, the chemical correlations of the Kraus school,³ in which the effort has been made to associate every-day medical problems with the chemical status of the individual person, seem to us to have been of greatest value. They took origin in earlier work of American physiologists. When one turns to problems of constitution,

1 Eppinger, H., and Hess, L. *Ztschr. f. klin. Med.* 68: 205 and 230, 1909.

2 Schade, H. *Physikalische Chemie in der inneren Medizin*, ed. 3, Dresden, Theodor Steinkopff, 1923.

3 Kraus, F. *Allgemeine und spezielle Pathologie der Person*. I. Tiefenperson, Leipzig, Georg Thieme, 1926.

it is particularly Bauer⁴ who has emphasized the practical value. In this country, it is Draper⁵ who has sought to extend a wider appreciation of the medical importance of constitutional reactivity.

It is inflammation with which one is, after all, chiefly concerned. Whether one studies it in its physiologic approaches, as one can very readily in digestive activity, whether in the exaggerated or peculiarly modified manifestations apparent in allergy, whether in default, as it may be in severe infections, the fundamental components that control the phenomenon must be similar, must be amenable to control and, therefore, must be therapeutically approachable by other than specific measures. The fundamental components engaged include the local cell mass, the mobile cells, the vascular tissues, the autonomic nerves and the chemical and hormonal influences of the humoral milieu. The innumerable variations possible with so many variable factors operative in the process readily account for the different types of inflammatory reactions with which one has to deal clinically.

The emphasis on the etiologic factor in inflammation which resulted from the development of bacteriology, for a time over-shadowed any interest in factors that might inherently modify the inflammatory reaction. Only in relatively recent times does one find investigation dealing, for instance, with the modification of inflammation as the result of preexisting inflammatory processes (tuberculosis, for example), the change in the blood chemistry under such conditions or the gradual alteration of the autonomic responses.

The particular studies that are made the basis for this, as well as the subsequent related papers, have as their background the considerations outlined in the preceding paragraphs. We have taken a group of 100 so-called normal men and have endeavored to see what relation their reactions to a stimulus or an injury—blister, Kromayer lamp burn, ice, injection of epinephrine hydrochloride, pharmacologic intracutaneous injections, etc—might bear to previous disease (tuberculosis, syphilis, infections), the blood chemistry, the basal metabolic rate, the age, the weight, etc.

There are many factors that limit the value of conclusions drawn from such work. In the first place, averages made from only 100 individual reactions are by no means satisfactory. The normal individual variations in many of the reactions are large. The possibility of error in the determination of many of the reactions themselves cannot be excluded, chiefly in such determinations as that of the basal metabolic rate. The practical inability to secure duplicates, due to the

⁴ Bauer, J. *Konstitutions und Vererbungslehre*, ed. 2, Berlin, Julius Springer, 1923, *Klin. Wchnschr.* 8:145, 1929.

⁵ Draper, George. *Human Constitution*, Philadelphia, W. B. Saunders Company, 1924.

fact that only one examination was feasible and that the amount of blood that could be taken without arousing resentment was limited, does not afford the feeling of accuracy that we might desire. These were factors that we could not alter, however much we might deplore them.

The persons examined were presumably "normal" men. That is to say, they were not patients of the hospital. About twenty were men employed about the hospital and laboratories as technicians, the rest were unemployed men who were sent to us from the state employment bureau. They ranged in age from 20 to 76, some were undernourished, some were chronic users of alcohol. A large percentage showed definite evidence of cardiorenal vascular damage of some degree. We felt that the group afforded us sufficient variation in reactivity because of their environmental conditions. We have not included women in the study lest the profound biologic alterations associated with the sex cycle⁶ should introduce more factors difficult to evaluate and control.

EXAMINATIONS MADE

The men reported to us at eight in the morning, having been instructed to come without breakfast. In a few instances, they had had alcoholic stimulants the night before. Some were apprehensive and nervous, and the examination of the basal metabolic rate was undoubtedly unsatisfactory on that account. They were kept under observation the entire day, during which they were given a luncheon at noon.

The examinations made included the following:

1 The blood chemistry: calcium by the method of Clark and Collip,⁷ potassium by the method of Kerr,⁸ CO₂ combining power, sugar (Folin-Wu), cholesterol by the Bloor, Pelkan and Allen^{8a} modification of the Bloor method, globulins by the method of Rohrer,⁹ and total protein by the refractometric method.

2 The skin blister by the cantharides method,¹⁰ with determination of the relative permeability of the capillaries, and determination of the blister time.

6 Petersen, W. F., and Milles, G. The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, *Arch Int Med* **38** 730 (Dec) 1926.

7 Clark and Collip. *J Biol Chem* **63** 461, 1925.

8 Kerr, J. *Biol Chem* **67** 689, 1926.

8a Bloor, W. R., Pelkan, K. F., and Allen, D. M. *J Biol Chem* **52** 191, 1922.

9 Rohrer. *Deutsches Arch f klin Med* **121** 221, 1926.

10 Petersen, W. F., and Willis, D. A. Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch Int Med* **38** 663 (Dec) 1926.

3 The basal metabolic rate and the weight/length ratio (weight in pounds, length in inches)

4 Reactions to the subcutaneous injection of epinephrine hydrochloride, as shown by pulse rate and blood pressure In the charts, the increase or decrease in the average pulse pressure for one hour after the injection is recorded in terms of the percentage of the pre-injection level A calculation was also made of the so-called cardiac output (pulse pressure \times pulse rate), and the percentage of increase or decrease recorded

5 The reaction to the Kromayer lamp, as shown in the time of appearance of erythema following an application of the light for thirty seconds to the forearm

6 The reaction to ice, as revealed in the time of appearance of erythema following an application of ice to the chest wall

7 The muscle reactions, as shown by the threshold of electric current that would provoke reactivity, in milliamperes

8 The resistance of the moist skin for direct current of low amperage This was determined in the following way

A storage battery (fig 1) of a potential difference of 2 volts was short circuited by a potentiometer of 730 Ω From one terminal and the sliding contact of the potentiometer, a variable voltage could be taken between 2 volts and zero and measured by a scale along the potentiometer wire This voltage was applied to the skin by two clay electrodes, soaked with 1 per cent saline solution The larger electrode was kept firmly by the left hand of the patient, the smaller electrode was placed on those parts of the left arm the resistance of which was to be determined (from two to three on the front) Usually points close to the center of the biceps and those between the elbow and the wrist at the flexor side were selected The resistance between the large electrode and the hand was negligible against the much larger resistance between the small electrode and the spots on the arm Any contact between the smaller electrode and an open wound made it evident that the resistance of the lower tissues (muscle, blood vessels, etc) was small as compared with the resistance of the skin A micro-amperemeter was inserted in this circuit, one scale division registering 0.24 micro-ampere All the readings were taken at scale division 10, i e., 2.4 micro-amperes, by adjusting the potentiometer till this constant current was reached This method employing constant current was preferable to the one employing constant voltage, because the resistance of the skin varied considerably, and sometimes, even with a low voltage, so much current was going through as to cause a burning, stinging pain, in this case, the current showed a tendency to go up gradually In preparation for the measurements, the skin was wet with saline solution and then dried gently, and the wet electrode put on The voltage was increased from zero to the one which gave a micro-amperage of 2.4 Exceptionally, the maximal voltage failed to cause the desired current to flow In this case, the resistance was figured out from the voltage 2 and the current of less than 2.4 micro-amperes Our figures for resistance are given in terms of megohms per square centimeter Usually five spots on the biceps and five spots on the lower arm were measured The measurements were made from three to

four times on the same day, early in the morning, right before and right after lunch and possibly later in the afternoon. This was important in order to get averages, and to gain an idea as to the variations that occur in the course of a day.¹¹ We have started investigations with the point of view of following up these variations of resistance more closely and in relation to other factors.

9 The reactions to intracutaneous injections (Hecht-Groer), as estimated by the average size of the wheal (diameter in millimeters) and

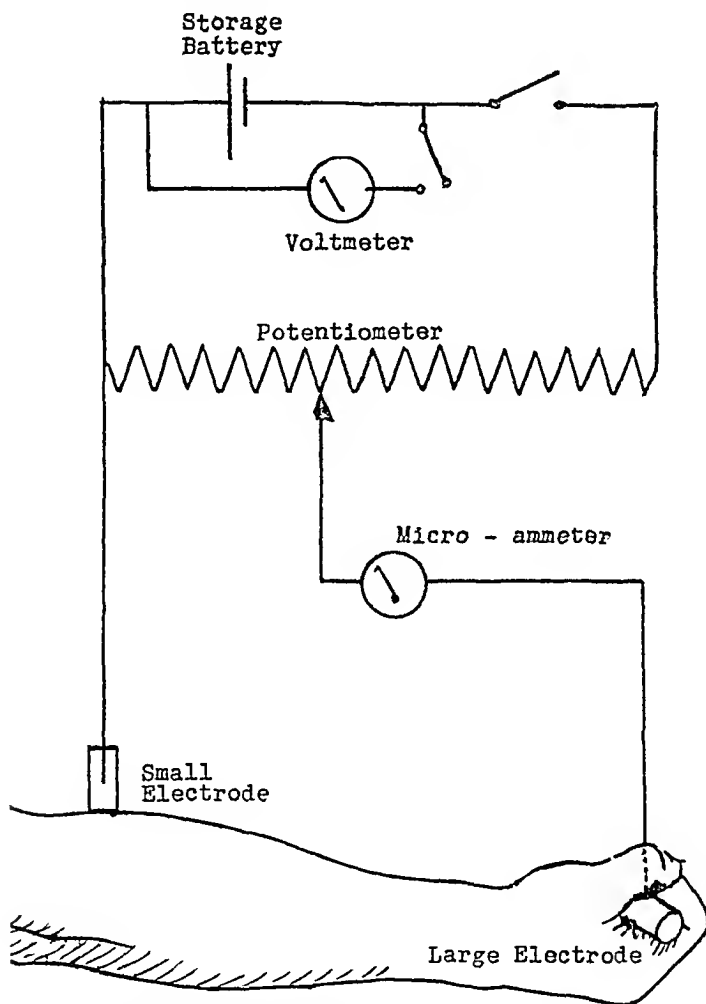


Fig 1—A diagram showing the method used in testing the resistance of the skin to electric current of low amperage

11 Some measurements were repeated the next day or a few days later, in order to control variations that might occur from day to day. Extensive measurements of this kind were reported by Curt P Richter (*The Electrical Skin Resistance. Diurnal and Daily Variations in Psychopathic and in Normal Persons*, *Arch Neurol & Psychiat* 19 488 [March] 1928). Richter found characteristic diurnal variations for certain classes of neurologic patients, daily variations occurred also, but they were small compared to the pronounced differences of the average resistance from one to another patient.

the flare (width of radium in millimeters) for (a) morphine (1 to 10,000,000 and 1 to 1,000,000), (b) epinephrine hydrochloride, 1 to 1,000, 1 to 10,000, 1 to 100,000 and 1 to 1,000,000, (c) thyroxin, 1 to 10,000, and (d) caffeine, 1 to 100

10 A roentgenogram of the chest to ascertain the presence of active or healed tuberculosis and the condition of the great vessels and heart

11 A physical examination and history, particular emphasis being laid on a history of sensitization and of previous infectious diseases, alcoholism, the amount of hard physical labor, etc

12 A Wassermann test

13 A urinalysis and examination of the skin capillaries

METHOD OF ASCERTAINING CORRELATIONS

In order to obtain a general survey of the large amount of statistical material obtained, we proceeded in the following manner

The results of each determination were arranged in arithmetical order. For instance, the individual cases were first arranged in the order of the time required for the formation of the blister, which varied from 35 to 15 hours. Four groups (twenty-five each) were then made, and the averages determined, the averages in this case being 58, 62, 79 and 102 hours. The averages were then recorded, and averages were determined and recorded for the results of the other examinations of the men thus grouped in order of increasing blister time. For instance, the corresponding averages for the time of the reaction to the application of the Kromayer lamp were found to be 127, 192, 24 and 236 hours, respectively, a sequence which might justify the supposition that some common factor is to be sought in the apparent coincidence of delay in the formation of the blister and delay in the appearance of the erythema. If, on the other hand, the averages for the results of the other examinations revealed no consistent progression or regression, we felt justified in assuming that no important correlation existed.

In table 1, we therefore present the average figures for each determination arranged in sequence, the four figures in each compartment indicating the averages of the four groups of twenty-five each.¹²

The heavy arrow has been inserted to show the direction of progression of the values for each key subject under consideration. Thus, column 1 indicates the average blister time of the four groups, and in reading down, the averages for the other determinations will be found. The lighter arrows indicate a probable correlation with the key sub-

¹² Only the group arrangements for the flares of the reactions to thyroxin and caffeine differ. Fifty-six persons have no thyroxin flares, the results for the rest were arranged in sequence. Sixty-four persons showed no caffeine flares. The results for the thirty-six who showed flares were arranged in sequence in three groups of twelve each.

ject under consideration. Thus in column 1 some apparent relation exists between the calcium level, the potassium level, the K/Ca ratio, etc., and the subject under consideration, i.e., the blister time.

BLISTER TIME (TABLE 1, COLUMN 1)

The average blister time for the 100 men was 7.5 hours. In previous communications,¹³ we called attention to the fact that the blister time of a person may vary considerably, being uniformly short in the exophthalmic patient and prolonged in patients with certain types of renal disease. In our use of the method, the plaster was removed after six hours, and the time of appearance of the blister recorded on the basis of the time from the application of the plaster to the time when the first evidence of blistering was observed. A shortening of the blister time was apt to be overlooked by this practice, and our records, therefore, are more accurate for the cases showing prolonged blister time than for those showing a shortened blister time.

The averages of the blister time (in hours) for the four groups, as recorded in table 1 are

5.8	6.2	7.9	10.2
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Certain correlations with other determinations appear as follows:

Kromayer Lamp Reaction Time—The groups that had a long blister time showed a delay in the appearance of the erythema following application of the Kromayer lamp for 30 seconds, as follows (hours):

- 1.27 (ranging from 45 min. to 3 hrs.)
- 1.92 (ranging from 50 min. to 5 hrs., 50 min.)
- 2.4 (ranging from 1 hr., 10 min. to 8 hrs.)
- 2.36 (ranging from 1 hr., 25 min. to 4 hrs., 50 min.)

As the erythema is probably due to the liberation of toxic substances from the injured cells of the skin area (Lewis¹⁴), one might anticipate some correspondence. The agreement of the two reactions is confirmed when the cases are arranged according to the Kromayer lamp reaction time (column 9).

Basal Metabolic Rate—With increasing blister time, the basal metabolic rate is lowered, but the sequence of regression is not perfect.

11.8	5.9	(9.8)	5.3
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A general agreement with this trend is found in column 10.

¹³ Petersen, W. F. The Permeability of the Skin Capillaries in Clinical Conditions, Arch. Int. Med. 39:19 (Jan.) 1927.
¹⁴ Lewis, Thomas. Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

20 4	Potassium (mg)	20 6 ↑ 21 4 20 3 10	19 6 ↑ 20 6 20 4 19 7	19 1 ↓ 20 8 20 8 20 9	19 1 21 19 7 19 2	16 8 ↓ 18 2 20 4 25 7	16 5 ↓ 18 6 20 5 24 5	19 5 21 1 19 9	19 7 20 1 19 6	20 2 20 0 19	19 7 20 5 19 7 20 8	20 1 20 6 20 6 19 7
2	K/Ca Ratio	2 09 ↑ 2 09 2 03 1 75	2 06 ↑ 1 95 1 93	1 91 ↓ 2 06 2 03	2 2 ↑ 1 82 1 6	1 58 ↓ 1 9 2 08 2 55	1 45 ↓ 1 51 2 15 2 66	1 9 1 87 2 03 1 9	1 97 2 00 2 08 2	1 99 2 02 1 9	1 95 2 2 2 05	2 06 ↑ 1 27 1 99 1 9
71	Sugar (mg)	71 71 71 2	70 73 70	73 70 71 70	67 73 71 73	72 1 70 2 73 2 73 5	71 68 73 72	60 68 74 02	69 69 72 72	70 9 72 4 69 8 68 9	70 72 75 67 4	69 3 71 75 8 71 2
2	Albumin/Globulin Ratio	2 01 ↑ 2 22 1 13	1 74 ↓ 2 56 2 42	1 4 2 5 1 81 2 3	1 9 2 2 1 76 2 2	1 84 2 20 1 88 1 88	1 89 1 8 2 1 2 2	1 86 1 73 2 2 2 1	1 1 1 6 2 08 3 3	1 86 2 10 1 8 2 03	2 1 1 93 1 2 1 76	1 9 1 96 1 88 2 10
2	Kromeyer Time (hours)	1 27 ↑ 1 92 2 4 2 36	2 02 ↓ 1 93 2 03 2 42	2 24 ↓ 2 23 1 92 1 92	1 85 2 2 1 87 2 1	1 86 1 8 2 08 2 28	2 09 1 4 2 1	2 1 1 93 1 94 2 32	1 87 2 22 1 7 2 5	1 24 ↓ 1 59 1 95 3 3	2 25 ↓ 2 06 2 18 2	1 8 2 01 1 7 2 73
+ 8	Basal Metabolic Rate	11 8 ↑ 5 9 9 8 5	10 5 8 5 12 4 8	6 3 7 11 10	12 8 2 10 9 3	15 7 5 8 4 13 2	11 7 4 9 12	13 5 1 7 2	8 4 8 4 9 9 4	9 7 ↑ 7 5 8 4 8 1	-0 9 ↓ 2 2 13 3 28	13 7 ↑ 8 7 8 4 5
46	Skin Resistance (M Ω)	51 38 43 53	44 44 40 51	37 ↓ 44 51 48	33 ↓ 48 42 63	46 46 50 37	65 ↑ 46 34 36	4 53 39 46	31 46 61 46	48 38 39 52	47 ↑ 62 3 3	14 ↓ 27 40 1 03
3 2	Muscle Reaction (M A)	3 3 3 23 3 1 3 2	3 4 2 5 3 5 3 28	2 85 3 5 3 2 3 23	3 4 2 68 3 3 3 3	3 4 3 4 3 5 2 66	3 1 3 5 3 2	2 8 3 26 3 95 2 9	2 9 3 1 4 0	3 2 3 6 2 7	3 2 3 2 3 08 3 3	3 6 ↑ 3 5 2 5 2 7
124	Systolic Blood Pressure	125 121 127 123	126 126 120 122	126 124 122 124	121 123 122 129	128 124 118 127	125 114 122 128	124 123 131 113	125 124 124 122	125 124 123 124	123 128 120 119	129 123 118 127
71	Diastolic Blood Pressure	71 71 72 70	72 69 72 72	72 67 73 71	70 73 70 68	72 72 71 72	72 70 70 72	71 67 75 72	72 72 70 70	72 70 69 69	72 73 73 67	70 71 63 76
72 5	Pulse Rate	70 72 74 74	74 70 73 72	76 70 73 72	71 73 70 76	75 71 70 75	77 70 72 73	72 73 72 73	72 74 72 66	67 75 70 72	72 73 70 72	72 74 72 73
53	Pulse Pressure	55 50 53 54	55 53 54 60	54 57 49 51	51 50 52 62	58 52 47 55	53 56 52 56	53 56 54 41	53 54 54 52	53 54 54 56	51 52 55 52	59 52 55 51
+ 14 %	Epinephrine, Pulse Pres sure	16 3 16 3 13 10 6	9 4 ↓ 12 17	10 2 11 16	13 9 13 7 13	9 4 9 4 18 6 16 3	7 5 10 8 14	8 5 14 19 18	13 6 5 12	16 12 13 2 10 2	14 5 15 7 13 13 3	11 15 14 14
+ 20 5%	Epinephrine, Pulse Pres sure x Pulse Rate	21 25 23 14 4	14 6 24 24	12 22 25 26	33 20 2 20 2 21 7	15 4 16 8 28 4 23 2	14 6 14 17 24	13 21 22 29	18 16 28 23	25 22 2 17 8	21 24 22 6 16 5	16 22 20 23
57 7	CO2 Combining Power	57 60 57 57 3	56 6 ↓ 57 59 1 57 8	56 5 ↓ 57 3 57 3 58	56 4 ↓ 57 8 57 5 57 9	56 7 ↓ 56 5 57 7 58 0	57 8 56 8 56 8 58 2	56 8 57 9 57 5 57 9	59 2 57 8 57 4 58	55 8 ↓ 57 8 58 58 8	57 2 ↓ 57 4 57 8 55 4	58 3 57 7 56 8 57 7
19	Ice Reaction (seconds)	16 20 19 21	18 23 19 19 4	20 20 19 18	16 8 ↓ 22 4 20 5	19 17 4 18 20	21 8 18 16 8 21	17 4 24 15 8 18 1	19 19 20 17	19 21 17 18 4	16 3 ↓ 19 3 20 4	22 16 18 20
46 5	Age	46 ↓ 44 43 53	51 ↓ 46 41	55 ↑ 47 1 39 4	48 3 46 48	50 48 46 45	51 46 44 47 8	50 44 45 48	49 4 47 42 46	46 48 47 48	48 45 7 46 46	50 46 47 46
217	Weight/Length Ratio	220 220 213 215	229 233 216 218	217 222 217 207	218 219 217 212	214 223 217 216	20 5 219 222	211 217 222	219 8 221 213 218	227 211 216 210	221 219 216 207	220 230 217 203
207	Cholesterol (mg)	231 173 213 215	228 230 216 214	218 217 220 226	217 203 206 227	208 232 218 222	215 220 220 229	208 220 216 218	207 228 216 220	231 211 213 218	220 230 215 229	215 222 229 215
19 2	Epinephrine, Wheal (m m)	22 2 10 8 19 6 19 2	20 19 6 19 6 20 0	19 6 13 2 19 6 20 24	17 2 ↓ 19 2 20	19 2 20 19 6	20 4 20 20	19 4 17 6 19 6 20	19 6 18 4 19 6 20	20 4 20 4 20 4 18 4	19 2 20 18 8 15 2	20 20 15 2 15 6
8 8	Epinephrine, Flare (m m)	8 4 9 2 8 6 8 8	8 4 9 0 9 2 8 2	8 6 8 6 8 6 9 4	8 6 9 2 10	9 8 6 8 6 9 4	9 8 4 8 8	7 6 8 4 8 4 9	8 2 9 9 2	9 2 9 8 8 8 2	8 4 9 8 8 4 8	8 4 8 8 8 4 9 6
12 4	Morphine, Wheal (m m)	11 2 11 8 15 8 11	12 8 11 2 12 11 2	11 2 10 6 11 6 12 4	10 8 10 6 12 11 4	11 6 10 8 12 11 4	11 2 12 11 2 11	11 4 11 11 2 11 4	11 6 11 11 6 11 4	12 2 10 6 11 6 11	10 6 12 12 4 10 4	11 6 11 8 11 11 4
15 6	Morphine, Flare (m m)	1 4 16 2 15 4 15 6	15 8 16 4 16 16	15 2 16 8 15	14 2 16 15 2 16 6	15 6 15 8 15 2 16	16 4 15 2 17 6 15 6	14 17 4 15 6 16 2	14 16 17 15 4	15 6 16 4 16 14 2	15 16 16 14 2	14 16 16 4 16 4
11 2	Thyroxin, Wheal (m m)	11 9 4 10 2 11 8	11 11 4 11 6 11	11 2 10 6 10 6 10 6	12 2 11 2 12	12 2 11 6 11 6 9 2	12 4 14 4 11 6 10 6	12 11 10 8 11 6	11 11 6 11 6 12 6	11 2 11 4 11 6 10 6	13 10 6 11 4 10 2	10 8 10 4 11 2 12
4 8	Thyroxin, Flare (m m)	4 6 5 4 5 6	4 4 4 6 5 2 5 8	4 6 5 2 3 8	5 6 5 2 5	6 4 4 4 2 8	6 6 4 8 3 6 4 6	5 4 5 4 4 8 4 2	3 8 5 4 4 2	3 2 5 8 4 8	5 8 5 2 3 6	3 4 5 2 5 6
17 6	Caffein, Wheal (m m)	19 2 17 2 20	17 4 18 2 17 19	17 2 18 2 17 2 15 4	21 14 6 16 6 19 6	20 4 18 6 11	21 6 18 2 17 4	21 2 17 6 16 8 17 4	16 8 18 6 19 2	18 15 19 18 4	19 2 15 6 16 17 4	18 16 2 18 6 17 9
2 7	Caffein, Flare (m m)	2 4 1 8 2 6 4	1 4 ↓ 3 4 2 8	2 8 2 8 2 6 2 8	3 4 1 4 3 2 2 8	2 8 4 8 3 1 6	3 3 2 3 2	2 8 4 2 2 2 2	1 6 2 8 3 6 4 4	1 6 4 8 3 6 2	2 3 4 6 1 4	2 8 2 6 3 2 2

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Age—Age plays some rôle, the group showing the prolonged blister time being somewhat older, although the individual variations in the four groups are large

46 yr (26-68)	44 yr (25-66)	43 yr (28-79)	53 yr (22-73)
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When the results are arranged on the basis of age (column 19), the oldest age group again shows prolongation of the blister time. It is to be kept in mind that the oldest age group will show greater vascular-renal damage.

Calcium, Potassium and K/Ca Ratio—The prolonged blister time seems to be associated with a higher level of the blood calcium, as is evident in the following values:

10	10.1	10.1	10.5
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The corresponding values for potassium are in inverted order:

20.6	21.4	20.3	18
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The K/Ca ratio is, as a result, much lower in the group showing prolonged blister time:

2	2.19	2.01	1.71
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Globulin—The group with prolonged blister time also has the greatest amount of serum globulin. The corresponding averages for the albumin/globulin ratios are:

2.1	2.22	2.18	1.73
-----	------	------	------

This may be checked in column 8.

Summary—An analysis of the material indicates that the group with prolonged blister time is somewhat older, has more globulin, more calcium and a lower K/Ca ratio and is less responsive to the Kromayer lamp.

PERMEABILITY (COLUMN 2)

The average index of capillary permeability for the entire group is 62. In our previous communications, we pointed out that the permeability of the capillaries, as measured by the blister method, is increased in certain persons, i. e., in those with exophthalmic goiter (13), in those with severe intoxications (13), in sympathicotonic persons (15), etc. On the other hand, we noted that athletes tended toward a lower permeability (10), as did persons with certain types of lesions of the kidneys (13).

When the material now under consideration is grouped into the four groups of twenty-five each, the averages are found to be:

52 (46-56)	58 (56-61)	65 (61-70)	75 (70-91)
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When the determinations are so grouped, the following correlations seem of interest

Age—Age apparently has a direct relation. The corresponding averages of the ages are

51	50	46	41
(22-76)	(27-70)	(26-79)	(20-73)

It is obvious that all ages are represented in each group, nevertheless, the sequence is sufficiently good to seem of some significance (confirmed in column 19)

Weight—Slender persons seemingly have the more permeable capillaries. The corresponding averages of the weight/length ratios are

229	233	216	218
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The confirmation in column 20 is good

Reaction to Epinephrine—In a previous paper,¹⁵ we showed that so-called sympathetotonic persons have an increased permeability of the capillaries. In this grouping, it may also be observed that with increasing permeability, there is increased sensitivity to epinephrine. The values for the pulse pressures on injection of epinephrine hydrochloride averaged (per cent)

+94	+16	+12	+17
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A confirmation of this appears in column 15

Pulse Pressure—With increasing permeability, the pulse pressure seems to diminish somewhat, the averages being

55	53	54	50
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corresponding to a slight decrease in systolic blood pressure

Reactions to Intracutaneous Injection of Thyroxin and Caffein—The flares of the reactions to thyroxin and caffein increase with increasing permeability (columns 27 and 29 may be compared with column 2 here)

Summary—The apparent correlations are, therefore, with the age of the person, the weight/length ratio, the reaction to epinephrine, the pulse pressure and the radii of the thyroxin and caffein flares

INFLAMMATORY INDEX (COLUMN 3)

In a previous study,¹⁰ we sought to define an inflammatory index on the basis of the two determinations just discussed, i. e., the blister time and the permeability of the capillaries. Presumably, the degree of inflammation might be regarded as most intense if the rapidity of the

15 Petersen, W. F., and Levinson, S. A. The Relation of the Reaction to Epinephrine to Potassium-Calcium Ratio and Other Ratios, Arch. Int. Med. **42** 256 (Aug.) 1928

reaction and the degree of protein passage through the vessels were taken into consideration. We therefore used the ratio permeability/blister time as an index and used the term inflammatory index for the quotient

The average inflammatory index of the 100 men is 8.2

$$\frac{62 = \text{average permeability}}{7.5 = \text{average blister time}}$$

The averages for the four groups are

5.7	8	9.4	10.9
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The blood chemical correlations are evident

Potassium Level —

19.1	19.1	20.8	20.9
------	------	------	------

K/Ca Ratio —

1.9	1.9	2.06	2.03
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CO₂ Combining Power —

56.5	57.3	57.3	58
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These correlations are confirmed in columns 5, 6 and 17, respectively, though the confirmation in the latter case is only partial

Albumin/Globulin Ratio — Only the group with the low inflammatory index seems to have an increased amount of globulin, the ratios being

1.4	2.5	1.8	2.3
-----	-----	-----	-----

and this is confirmed when the tabulations for globulin are examined (column 8)

Other Correlations — The relation of age (the inflammatory index decreasing with age) seems certain, the relation of the weight/length ratio (a higher inflammatory index being found in the more slender subjects) is doubtful because it is not confirmed in column 20, and the correlation with the reactions to epinephrine is also uncertain for the same reason (columns 15 and 16). On the other hand, the resistance of the skin to electric current increases with increase in the inflammatory index, while the Kromayer lamp erythema time has a reverse relation (confirmed in column 9)

Summary — We seem to be justified in the assumption that the inflammatory reaction to cantharides is inhibited by advancing age and is more intense with higher levels of potassium and higher values of the K/Ca ratio. The Kromayer lamp reaction time is comparable. There is a probability that the more slender persons and the persons with the more marked reactions to epinephrines have a more intense inflammatory reaction. Curiously enough, there appear to be no correlations

with the intracutaneous reactions to pharmacologic substances except that to thyroxin. This diminishes with increase in the inflammatory index (column 26)

CALCIUM (COLUMN 4)

The average calcium value for the 100 men is 10.17. The average calcium values for the four groups are

9.2	9.7	10.8	12.2
(from 7.4-9)	(from 9.2-10.3)	(from 10.4-11.4)	(from 11.4-14.5)

Blister Time—The relation to the blister time has been discussed

Sugar Level—There appears to be some relation to the sugar level, the persons with low calcium level having a lower sugar level (confirmed in column 7). The differences are not, however, great

67	73	71	73
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Resistance of the Skin to Electric Current—A relation to the resistance of the skin to electric current seems probable (although the confirmation in column 11 is not convincing)

0.33	0.48	0.42	0.63
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Reaction to Ice—With an increasing amount of calcium, the reaction to ice is retarded (confirmed in column 18)

16	16.8	22.4	21.5
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Pulse Rate, Systolic Blood Pressure, and Pulse Pressure—With increasing amounts of calcium, the pulse rate increases

71	73	71	76
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but the confirmation in column 14 is not good. The systolic blood pressure increases as follows

121	123	122	129
-----	-----	-----	-----

but here, again, the confirmation (column 13) is not clear. The increase in the pulse pressure is more marked

51	50	52	62
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As no tabulation was made on the basis of pulse pressure, no confirmation is possible

CO₂ Combining Power—A possible correlation exists with the CO₂ combining power, which increases as follows

56.4	57.8	57.5	57.9
------	------	------	------

These differences are not great, but appear to be confirmed in column 17, where the calcium values increase with increasing CO₂ values

Skin Reactivity—The calcium column is the first in which we begin to find some correlations with the reactions of the skin to injections of pharmacologic substances. The wheal caused by the injection of epinephrine hydrochloride increases progressively as follows

17.2	19.2	20	20
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The flare of the reaction to epinephrine also increases

8	8.6	9.2	10
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A confirmation of these increases is had in columns 22 and 23

Summary—The correlations of the level of the blood calcium are, therefore, with the following: blister time, blood sugar level, the resistance of the skin to electric current, the reaction to ice and the diameters of the wheal and flare of the reaction to epinephrine, and probably with the following: pulse rate, systolic blood pressure and pulse pressure, and CO₂ combining power

POTASSIUM (COLUMN 5)

The average value of the blood potassium for the 100 men is 20.4. The fluctuations in the individual person's level of blood potassium are greater, as is well known, than those of the level of the calcium, changes of several milligrams per hundred cubic centimeters taking place during the course of the day. The normal range of values, too, is much greater, being from 13.4 to 28.8 mg. in our group.

Our four groups average

16	18.2	20.4	25.7
(13.4-17.4)	(17.4-19)	(19-22.8)	(22.8-28.8)

Inflammatory Index—The relation of the inflammatory index has already been mentioned.

CO₂ Combining Power—With increasing potassium values, the CO₂ combining power appears to increase.

56.7	56.5	57.7	58.8
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The confirmation in column 17 is, however, not striking.

Age—The sequence is suggestive.

50	48	46	45
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The expected confirmation in column 19 is, however, lacking.

Reaction to Epinephrine—The pulse pressure shows a percentage increase with increasing amounts of potassium.

9.4	9.4	18.6	16.3
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The pulse pressure \times the pulse rate shows a percentage progress as follows

15.4	16.8	28.4	23.2
------	------	------	------

which is confirmed for the pulse rate in column 15.

Muscle Reaction—The group averages are

3	3.4	3.6	2.66
---	-----	-----	------

a rather irregular sequence, but the control (column 12) is somewhat clearer

21.9	19.6	20.5	18.7
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Reaction to Thyroxin—The most convincing correlations are those with the reactions of the skin to intracutaneous injections of thyroxin and caffeine. The wheals average (in millimeters)

12.2	11.4	11.6	9.2
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This correlation is confirmed in column 26. The flares in the four groups average (in millimeters)

6.4	5.6	4.4	2.8
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and this is confirmed in column 27

Reaction to Caffein—The wheals due to caffeine show in similar relation

20	20.4	18.6	11
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confirmed in columns 28 and 29. The flares average

2.8	4.8	3	1.6
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Summary—Apart from the distinct relation to the inflammatory index, the potassium values influence the reactions to epinephrine and the reaction of the skin to thyroxin and caffeine, their relation to the CO_2 combining power, the muscle reaction and age are less certain

THE K/CA RATIO (COLUMN 6)

The average value of the K/Ca ratios of the 100 men is 2. The averages for the four groups are

1.45	1.81	2.35	2.66
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Blister Time, Inflammatory Index—The relations to the blister time and the inflammatory index have been discussed

Resistance of the Skin—A striking association exists with the resistance of the skin to electric current, the averages for which, in this grouping, are

0.65	0.48	0.34	0.35
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i.e., the groups with the increased K/Ca ratio have diminished resistance

Reactions to Epinephrine—The pulse pressures in the four groups average (per cent)

7.5	10	8.5	14
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The values of the pulse pressure \times pulse rate average (per cent)

14.6	14	17	24
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This correlation is confirmed in columns 15 and 16

Weight/Length Ratio—The thinner persons have a lower K/Ca ratio

205	219	217	222
-----	-----	-----	-----

Confirmation of this is had in column 20

Cholesterol Level—Those with low K/Ca ratio also appear to have less blood cholesterol

215	220	218	229
-----	-----	-----	-----

This is confirmed in column 21

Skin Reactions—As might be expected from the potassium relations, the parallelism to the reactions of the skin to thyroxin and caffeine is suggestive

Summary—The K/Ca ratio may, therefore, be regarded as of importance in connection with the blister time, the inflammatory index, the electrical resistance of the skin, the reactions to epinephrine, the weight/length ratio, the level of cholesterol and the reactions of the skin to thyroxin and caffeine

BLOOD SUGAR (COLUMN 7)¹⁶

The average of the blood sugar levels of the entire group is 71

The four groups have the following averages

60	68	74	82
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Calcium Level—The possible relation of the calcium level has been discussed

Reactions to Epinephrine—The most apparent correlation is with the reactions to epinephrine. The increase in pulse pressure for the groups is (per cent)

85	14	12	18
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and the "cardiac output" (per cent) is

13	21	22	29
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This correlation is confirmed in columns 15 and 16

Weight/Length Ratio—As the sugar increases, the weight also increases

205	219	217	222
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This is confirmed in column 20

The Flares Caused by the Intracutaneous Injection of Epinephrine Hydrochloride—The averages for the groups are (in millimeters)

76	84	84	9
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This correlation is confirmed in column 23

¹⁶ The sugar values are for serum

Summary—The following correlated factors are, therefore, to be considered The level of the blood calcium, the sensitivity to epinephrine, the weight/length ratio and the reaction of the skin to epinephrine

ALBUMIN/GLOBULIN RATIO (COLUMN 8)

The average value of the albumin/globulin ratio for the entire group is 2 The averages for the four groups are

1 1	1 6	2 08	3 3
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Blister Time—It has been previously noted that increasing blister time is associated with an increased amount of globulin This seems confirmed by the fact that the first group under consideration here with a ratio of 1 1 has a blister time of nine hours

Muscle Reactivity—A good correspondence is found

2 9	2 8	3 1	4
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and this correspondence is confirmed in column 12

Reactions of the Skin to Epinephrine and Thyroxin—The amount of flare due to the epinephrine is apparently associated

8	8 2	9	9 2
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This association is confirmed in column 23

The averages for the wheals caused by the intracutaneous injection of thyroxin are

11	11 6	11	12 6
----	------	----	------

These seem related (confirmed in column 26), as also those for the flares caused by thyroxin and for the wheals caused by caffeine

Summary—An increased amount of globulin is, therefore, probably related to an increased blister time, to an increased muscle irritability and to the reactions of the skin to epinephrine, thyroxin and caffeine

KROMAYER LAMP ERYTHEMA TIME (COLUMN 9)

For the 100 men, the average time of the appearance of the erythema from the time of application of the Kromayer lamp is 2 hours The averages for the four groups are (hours)

1 24	1 58	1 95	3 3
(75 min)	(96 min)	(117 min)	(200 min)

Blister Time and Inflammatory Index—The parallelism with the blister time and the inflammatory index has been discussed

Calcium Level—The apparent relation to calcium is

10 3	10 1	9 9	9 7
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but there is no confirmation in column 4

CO₂ Combining Power—The relation to the CO₂ combining power may be seen in the following averages

55.8	55	58	58.8
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This correlation is confirmed in column 17

Wheal Caused by Epinephrine—The averages are

20.4	20.4	20.4	18.4
------	------	------	------

Only the group with the long latent period appears to have some relation to the smaller wheal, the confirmation of this being found in column 22

Summary—The associations of the time of the erythema due to application of the Kromayer lamp appear to be the following the blister time, the inflammatory index, the CO₂ combining power and the diameter of the wheal caused by epinephrine

BASAL METABOLIC RATE (COLUMN 10)

The average basal metabolic rate for the entire number is +8 The averages for the groups are

-8.9	+2.2	+13.3	+28
------	------	-------	-----

Reaction to Ice—The reaction to ice as shown in the following averages, clearly parallels the basal rate

16.3	19.3	20	20.4
------	------	----	------

and the parallelism in column 18 is equally good

Resistance of the Skin to Electric Current—As the basal rate increases, the resistance of the skin to electric current appears to decrease, although the sequence is not perfect

0.47	0.39	(0.62)	0.3
------	------	--------	-----

Weight/Length Ratio—A correlation appears to exist with the weight/length ratio, the more slender persons having the higher rate

221	219	216	207
-----	-----	-----	-----

This is confirmed in column 20

Skin Reaction—The wheal due to epinephrine diminishes with the increased metabolic rate

19.2	20	18.8	15.2
------	----	------	------

This is confirmed in column 22

Summary—The basal metabolic rate, therefore, appears to be correlated with the electrical resistance of the skin, the reaction to ice, the weight/length ratio and the diameter of the wheal due to epinephrine

RESISTANCE OF THE SKIN TO ELECTRIC CURRENT (COLUMN 11)

The average resistance for the 100 men is 0.46 megohms per square centimeter The averages for the four groups are

0.14	0.27	0.40	1.03
------	------	------	------

Inflammatory Index, Calcium, K/Ca Ratio and Metabolic Rate—The parallelisms here have been discussed

Muscle Reaction—A higher resistance of the skin appears to be associated with a lower threshold response of the muscle, the averages being

36	35	25	27
----	----	----	----

This association is confirmed in column 12

Weight/Length Ratio—The thinner persons have a high resistance

220	230	217	200
-----	-----	-----	-----

This is confirmed in column 20

Skin Reaction—The flare due to epinephrine increases with the resistance of the skin to electric current

84	86	84	98
----	----	----	----

This is confirmed in column 23

The flare caused by thyroxin averages

34	52	52	56
----	----	----	----

The correlation is confirmed in column 27

Summary—The resistance of the skin to electric current has associations with the inflammatory index, the K/Ca ratio and the level of calcium, the metabolic rate, the muscle reaction, the weight/length ratio, the amount of flares due to epinephrine and thyroxin, and possibly the permeability of the capillaries

MUSCLE REACTIVITY (COLUMN 12)

The average for the muscle reactivity of the whole number is 32 milliamperes. The averages for the four groups are

17	23	366	61
----	----	-----	----

Albumin/Globulin Ratio and Skin Resistance—The relations here have been discussed

Pulse Rate—The pulse rate diminishes as the muscle reactivity diminishes

78	74	68	70
----	----	----	----

This relationship is checked in column 14

CO₂ Combining Power—One should anticipate a distinct decrease in the CO₂ combining power with decreasing reactivity. The results recorded in the table, however, indicate the opposite. The control is also irregular

Weight/Length Ratio—The weight/length ratio increases with the muscle reactivity

207	221	228	224
-----	-----	-----	-----

This increase is confirmed in column 20

Reaction to Caffein—The wheal due to the intracutaneous injection of caffein increases in diameter with increase in muscle reactivity

158	188	(174)	196
-----	-----	-------	-----

The parallel increase is checked in column 28

Summary—In addition to the correlations with the albumin/globulin ratio and the skin resistance, correlations with the following seem possible the pulse rate, the weight/length ratio and the diameter of the wheal due to caffein

SYSTOLIC BLOOD PRESSURE (COLUMN 13)

The average blood pressure for the whole number is 124 systolic and 71 diastolic. The averages for the four groups are

104	118	128	146
-----	-----	-----	-----

Diastolic Blood Pressure and Pulse Pressure—Naturally the diastolic blood pressure corresponds

62	70	72	76
----	----	----	----

as well as the pulse pressure

42	58	56	68
----	----	----	----

Reaction to Epinephrine—The pulse pressure, as well as the pulse pressure \times pulse rate, is distinctly associated with the systolic blood pressure, the averages being (per cent)

21	12	99	94
27	20	18	16

Age—The age increases with the systolic pressure

45	(43)	46	54
----	------	----	----

This correlation is checked in column 19

Reaction to Caffein—The flare diminishes

76	3	22	38
----	---	----	----

This is confirmed in column 29

Summary—The associations (apart from those with diastolic and pulse pressure) apparently are with the following the reaction to epinephrine, the age and the radius of the flare due to the intracutaneous injection of caffein

PULSE RATE (COLUMN 14)

The average pulse rate for the 100 men is 72.5. The averages for the four groups are

60	69	76	86
----	----	----	----

Calcium Level and Muscle Reaction—The relations here have been discussed

Reaction to Epinephrine, CO₂ Combining Power—The apparent correlations with the "cardiac output" following epinephrine injection and with the CO₂ combining power are not confirmed in columns 16 and 17

Reaction to Caffein—The averages for the wheal are

18	(194)	178	16
----	-------	-----	----

This relation is confirmed in column 28

Summary—The correlations appear to be with the following the level of calcium, the muscle reaction, the reaction to caffein, and possibly with the CO₂ combining power and the reactions to epinephrine

REACTIONS TO EPINEPHRINE EFFECT ON PULSE PRESSURE (COLUMN 15)

The average increase of the pulse pressures of the 100 men is +14.7 per cent during the hour following injection. The increase or decrease (per cent) for the four groups is

—3.5	+6	+16	+36
------	----	-----	-----

Permeability of Capillaries, Potassium Level, K/Ca Ratio, Sugar and Systolic Blood Pressure—The relations here have been discussed

Pulse Pressure—The persons with the greatest reaction to epinephrine are in the group who have the smallest pulse pressures before the injection

54	56	50	42
----	----	----	----

There is no confirmation here because no results are arranged on the basis of pulse pressure

Cardiac Output—The correlation is such as might be expected

Weight/Length Ratio—The more slender men show the greater reaction to epinephrine

225	216	215	197
-----	-----	-----	-----

This is partially confirmed in column 20

Summary—The chief correlations are, therefore, with the permeability of the capillaries, the potassium level, K/Ca ratio, the sugar level, the systolic blood pressure and the weight/length ratio

REACTIONS TO EPINEPHRINE (COLUMN 16) "CARDIAC OUTPUT" (PULSE PRESSURE × PULSE RATE)

The average increase of the "cardiac output" of the 100 men is 20.5 per cent. The increase (per cent) for the four groups following the injection of epinephrine hydrochloride is as follows

—1.7	+19	+24	+42
------	-----	-----	-----

K/Ca Ratio, Sugar, Reaction to Epinephrine (Pulse Pressure)—The correlations here have been discussed

CO₂ Combining Power—The correlation with the CO₂ combining power is good

57.4	57.8	57.9	59.5
------	------	------	------

but the control (column 17) does not check

Reactivity to Epinephrine—The flares averaged (in millimeters)

8.6	8.6	9.2	9.6
-----	-----	-----	-----

The control may be read in column 23

Summary—Only a few correlations can, therefore, be ascertained these are with the K/Ca ratio, the sugar level and the diameter of the flare due to epinephrine, and, possibly, with the permeability of the capillaries and the CO₂ combining power

CO₂ COMBINING POWER (COLUMN 17)

The average CO₂ combining power of the 100 men is 57.7 The averages for the four groups are

53.5	56.5	58	62.3
------	------	----	------

Kromayer Lamp Erythema Time—The correlations have been commented on previously

Reaction to Ice—The reaction time increases with the increase in CO₂ tension, the averages being as follows

17	20	19	19
----	----	----	----

The control (column 18) affords some support

Weight/Length Ratio—A distinct correlation exists here, the more slender men having a higher CO₂ combining power

229	218	210	212
-----	-----	-----	-----

Reaction to Thyroxin—The amount of flare of the reaction to thyroxin seems related

6.4	3.4	5	4.4
-----	-----	---	-----

The confirmation appears in column 27

Summary—The apparent correlations are with the weight/length ratio, the reaction to ice, the Kromayer lamp erythema time and the amount of flare in the reaction to thyroxin

ICE REACTION TIME (COLUMN 18)

For the 100 men, the average time of the reactions to ice is nineteen seconds The averages for the four groups are (seconds)

9	15	20	32
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Calcium, Basal Metabolic Rate, CO₂ Combining Power—The correlations with these have been discussed

Age—The relation to age is obvious

44	45	48	49
----	----	----	----

This relation is confirmed in column 19

Skin Reactions—A possible relation exists to the radius of the flare in the reaction to thyroxin and to the dimensions of both wheal and flare in the reactions to caffeine. The averages for the former are

5.8	5	5.4	2.6
-----	---	-----	-----

This is confirmed in column 27

The averages for the wheal and the flare of the reaction to caffeine are

20.6	18.2	18.8	14
2.4	2.2	3.4	3

These correlations are confirmed in column 28 and column 29, respectively

Summary—The correlations are, therefore, with the age, the level of the calcium, the basal metabolic rate, the CO_2 tension, the radius of the flare of the reaction to thyroxin and the dimensions of both the wheal and the flare of the reactions to caffeine

AGE (COLUMN 19)

The average of the ages of the 100 men is 46.5. The averages for the four groups are

30	42	51	65
----	----	----	----

Blister Time, Permeability of Capillaries, Inflammatory Index, Systolic Blood Pressure, Reaction to Ice—The correlations here have been discussed

Reaction to Caffeine—There is some indication that the diameter of the wheal increases with the age

14.6	13.4	21	21.4
------	------	----	------

The confirmation of this is in column 29

Summary—The correlations are with the blister time, the permeability of the capillaries, the inflammatory index, the potassium level, the blood pressure, the reaction to ice and the reaction to caffeine

WEIGHT/LENGTH RATIO (COLUMN 20)

The average of the weight/length ratios of the 100 men is 217. The averages for the four groups are

187	207	216	232
-----	-----	-----	-----

Permeability of Capillaries, K/Ca Ratio, Sugar Level, Basal Metabolic Rate, Skin Resistance, Muscle Reaction, Reactions to

Epinephrine and CO₂ Combining Power—The correlations here have been commented on

Cholesterol Level—The averages for cholesterol show a relation (confirmed in column 21) as follows

210	217	216	225
-----	-----	-----	-----

Skin Reactions—The diameters of the wheals in the reactions to epinephrine average (in millimeters)

188	188	196	20
-----	-----	-----	----

This correlation is confirmed in column 22

The flares of the reactions to the intracutaneous injection of morphine average (in millimeters)

148	15	166	158
-----	----	-----	-----

This parallel increase is confirmed in column 25

Summary—The correlations in this grouping are seemingly most extensive

CHOLESTEROL (COLUMN 21)

The average of the cholesterol values for the entire number examined is 207 The average for the groups are

181	219	202
-----	-----	-----

Only three groups were arranged because determinations of cholesterol were not made for the entire series

Correlations—The correlations are with the K/Ca ratio and the weight/length ratio It appears that the pulse pressure also bears some relation, diminishing as the cholesterol increases The correlations are, therefore, few

REACTIONS TO EPINEPHRINE THE WHEEL (COLUMN 22)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of epinephrine hydrochloride is 19.2 mm The averages for the groups are

168	17.6	20.4	22
-----	------	------	----

Calcium Level, Basal Metabolic Rate, Weight/Length Ratio, Kio-mayer Lamp Reaction Time—We have previously called attention to the possible correlations here

Pulse Pressure—The pulse pressure seemingly increases with the size of the wheel

51	50	56	56
----	----	----	----

No check is possible, however

Reaction to Caffein—The averages of the diameters of the wheals indicate a relation (checked in column 28)

(18)	20.2	19.4	13.2
------	------	------	------

Summary—The correlations are, therefore, with the calcium level, the basal metabolic rate, the weight/length ratio, the Kromayer lamp erythema time and the reactions to caffeine

REACTION TO EPINEPHRINE THE FLARE (COLUMN 23)

The average of the radii of the flares in the reactions of the 100 men to epinephrine is 8.8 mm. The averages for the groups are

5.8	8.8	10	11.6
-----	-----	----	------

Calcium, Sugar, Albumin/Globulin Ratio, Skin Resistance, Reaction to Epinephrine (Pulse Pressure \times Pulse Rate)—The correlations with these have been previously discussed

Reactions to Morphine Flare—The flares of the reactions to morphine show a parallel increase (checked in column 25)

13.2	15	16	16.6
------	----	----	------

Reactivity to Caffeine—The wheals in the reactions to caffeine also show a relation (checked in column 28)

18	19.4	18.6	14.4
----	------	------	------

Summary—The relations are, therefore, to the calcium level, the sugar level, the albumin/globulin ratio, the skin resistance, the reaction to epinephrine (pulse pressure \times pulse rate) and the reaction to morphine (flare) and to caffeine (wheal)

REACTION TO MORPHINE THE WHEEL (COLUMN 24)

The average of the diameters of the wheals in the reactions of the 100 men to intracutaneous injections of morphine is 12.4 mm. The averages for the four groups are

9	10.6	11.8	14
---	------	------	----

No correlations are found

REACTION TO MORPHINE THE FLARE (COLUMN 25)

The average of the radii of the flares in the reactions of the 100 men to morphine is 15.6 mm. The averages for the groups are

10	14.4	16.6	22
----	------	------	----

The correlation with the weight/length ratio has been referred to. The amount of flare in the reaction of the skin to epinephrine is apparently related

7.8	8.8	9.6	10
-----	-----	-----	----

REACTION TO THYROXIN THE WHEEL (COLUMN 26)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of thyroxin is 13.6 mm. The averages for the groups are

7.6	10.4	12	14.6
-----	------	----	------

Inflammatory Index, Potassium, K/Ca Ratio, Albumin/Globulin Ratio—The correlations here have been discussed

Reaction to Thyroxin (Flare)—The averages for the flares are

26	36	66	62
----	----	----	----

This may be checked in column 27

Reaction to Caffein—The averages for the wheals in the reactions to caffein are

86	19	22.2	20.6
----	----	------	------

for the flares

12	24	28	42
----	----	----	----

These parallel increases may be checked in columns 28 and 29, respectively

Summary—The correlations, therefore, are with the inflammatory index, the potassium level, the K/Ca ratio, the albumin/globulin ratio, the amount of flare in the reaction to thyroxin and the reaction to caffein (wheal and flare)

REACTION TO THYROXIN THE FLARE (COLUMN 27)

The average of the radii of the flares in the skin reactions of the 100 men to thyroxin is 4.8 mm. The averages for the four groups are

0	4.6	8.6	10.6
---	-----	-----	------

In this grouping, fifty-six men showed no reaction to the thyroxin. These fifty-six are represented by zero, the other three groups, consisting of 18, 19 and 19 men each, showed flares as set forth.

The averages for the wheals in the reactions to caffein (checked in column 28) are as follows

16.3	15	20.8	20.2
------	----	------	------

for the flares

0.8	4.6	2	5.8
-----	-----	---	-----

Correlations—Previously discussed correlations include those with the potassium level, the K/Ca ratio, the resistance of the skin to electric current, the reaction to ice, the reaction to epinephrine (wheal) and the size of the wheal in the reaction to thyroxin. It is to be noted that the caffein reaction is closely related.

REACTION TO CAFFEIN THE WHEAL (COLUMN 28)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of caffein is 17.6 mm. The averages for the four groups are

7.6	15.2	21.6	25
-----	------	------	----

If one classifies the men examined on the basis of the vascular reaction to epinephrine, one must conclude that vagotonic (lessened or negative) reaction to epinephrine is associated with prolonged blister time and prolonged Kromayer lamp erythema time

Permeability of the Capillaries, Inflammatory Index —We turn next to another factor of the inflammatory index, permeability of the capillaries. In table 3 a comparison of this factor with mineral balance and other factors is made. The relationship with the reaction time to the Kromayer light falls away because there is no apparent direct relationship between this and permeability of the capillaries. Here it again becomes evident that the K/Ca ratio, the CO_2 combining power, the

TABLE 3—*The Relations of Permeability of the Capillaries and Inflammatory Index to Mineral Balance and Other Factors*

	Permeability of Capillaries →	Inflammatory Index →
Calcium level	(?) →	
Potassium level		→
K / Ca ratio	←	←
CO_2	→	→
Muscle reaction		
Albumin / globulin ratio	→	→
Basal metabolic rate		←
Age	←	←
Vascular reaction to epinephrine	→	(→)
Skin reaction to epinephrine		
Skin resistance to electric current	→	→
Weight / length ratio	←	←
Reaction to thyroxin and caffeine (flares)	→	

albumin/globulin ratio, the age, the weight/length ratio and the resistance of the skin to electric current are related

From tables 1 and 3, it is obvious that permeability of the capillaries of the skin, while related to the K/Ca ratio, appears to be less under the influence of the actual concentrations of these elements. There is a clear relation to age, to the vascular responsiveness to epinephrine, to the resistance of the skin to electric current and to the weight/length ratio.

Variations of the endocrine status, particularly as concerns thyroid activity, are probably chiefly concerned. The younger person has presumably greater secretory activity, greater permeability of the capil-

laries and a more marked sensitivity to epinephrine. The width of the flares in the skin reaction to thyroxin and caffeine forms part of this picture¹⁷

In table 4 the various factors that have been examined are grouped as they relate to skin reactivity. When one examines this table, a number of consistent correlations immediately stand out.

The increase in permeability of the capillaries proceeds with an increase in the inflammatory index and in the flares due to epinephrine, thyroxin, caffeine and morphine (not shown in table).

Increase in the serum calcium is associated with (1) a prolonged reaction time to ice, but with a diminished reaction time to the Kromayer light, and (2) an increase in the size of the wheal and the flare due to epinephrine, but a decrease in the size of the wheal due to thyroxin. These contrary reactions to epinephrine and thyroxin have been observed previously¹⁷

Increase in potassium proceeds with (1) an increase in the inflammatory index, but is associated with a prolongation of the erythemas due to the application of the Kromayer light and ice, and (2) a decrease in the size of the wheals and flares due to thyroxin and caffeine.

Increase in the K/Ca ratio proceeds with (1) an increase in the inflammatory index, but a delay in the reaction to ice, and (2) an increase in the reactions to thyroxin and caffeine as the K/Ca ratio is lowered.

Increase in the CO₂ combining power of the serum (in the direction of an alkalosis) accompanies (1) increase in the inflammatory index and increase in the time of erythema due to the applications of the Kromayer light and ice, and (2) increase in the wheal due to epinephrine and decrease in the wheal due to thyroxin.

Increase in the basal metabolic rate accompanies (1) increase in the inflammatory index, shortening of the reaction to the Kromayer light and prolongation of the reaction to ice, and (2) decrease in the wheal and flare due to epinephrine.

As the weight/length ratio increases (in heavier persons), the wheal due to epinephrine increases in size, while the wheal due to thyroxin tends to diminish.

Table 5 presents the blood chemistry and its correlations with the weight/length ratio and other factors. When one examines this table on the basis of the weight/length ratio, one finds that as weight increases, four reactions may be grouped: 1. Permeability of the capillaries diminishes. 2. Potassium increases. 3. The K/Ca ratio increases. 4. The CO₂ combining power diminishes.

17 Petersen, W. F., and Levinson, S. A. IV. The Patient with Exophthalmos and the Nervous Patient, *Arch. Path.* (p. 267, this issue).

TABLE 4—*The Relations of the Various Factors Examined to Skin Reactions*

	Inflammatory Index	Reaction to Kromayer Light	Reaction to Ice	Skin Reactions					
				Epinephrine, Wheal	Epinephrine, Flare	Thyroxin, Wheal	Thyroxin, Flare	Caffein, Wheal	Caffein, Flare
Blister time	..	+	+	+
Permeability of capillaries	+	+	..	+	..	+
Inflammatory index		+	+
Calcium level	..	+			+	+
Potassium level	+	..	+	+	+	+	+
K / Ca ratio	+	..	+	+	+	+	+
CO ₂ combining power	+	+	+	+	..	+	+
Sugar level	+	+	+
Albumin / globulin ratio	-	+	+	+	+	+	..
Vascular reaction to epinephrine	+	+
Skin resistance to electric current	+	..	+	..	+	-
Basal metabolic rate	+	+	+	+	+
Muscle reaction	..	+	+	-	+	+	..
Blood pressure	+	..	+	+
Age	+	..	+	-	+	..
Weight / length ratio	+	..	+	+	+	..
Reaction to ice		+	+	+	+
Reaction to Kromayer light	+		-	+	..	-

TABLE 5—*The Blood Chemistry and Its Correlations with the Weight/Length Ratio and Other Factors*

	Weight / Length Ratio	Vascular Reaction to Epinephrine	Sugar Level	Muscle Reaction	Pulse Rate	Blood Pressure	Reaction to Epinephrine, Wheal	Reaction to Epinephrine, Flare	Reaction to Thyroxin, Wheal	Reaction to Thyroxin, Flare
Inflammatory index	-	-	..	-	+	-
Permeability of capillaries	+	+	+	+	+	+
Calcium level	-	..	+	..	+?	..	+	+	+	-
Potassium level	+	+	..	+	+	+
K / Ca ratio	+	+	..	+	+	+
CO ₂ combining power	+		+?	..	+	..	+	+
Albumin / globulin ratio	-	..	+	+	+	-	-	+	+	+
Basal metabolic rate	+	+	+
Skin resistance	+	..	-	+	+	..	-
Muscle reaction	+		+	+	-	+
Sugar level	+	+		+	+
Age	+
Weight / length ratio		+	+	+	..	+	+
Pulse rate	+		+
Blood pressure	..	+	+
Reaction to ice	..	-	+	..	+	+
Kromayer lamp erythema time	+
Vascular reaction to epinephrine	+		+	..	+	+	-	+?
Reaction to epinephrine, wheal	+	+	..
Reaction to epinephrine, flare	+		+	+
Reaction to thyroxin, wheal	-		+
Reaction to thyroxin, flare	-	..	+	-	+	..	+	

This group of chemical correlations is distinctly related to the wheal and flare due to thyroxin, both of which diminish with increasing weight

With the increase in weight, the second group of reactions is to be studied 1 The basal metabolic rate diminishes 2 The resistance of the skin to electric current increases 3 The muscle reactivity diminishes 4 The sugar increases

This second group of reactions is not so closely related to the K/Ca ratio (muscle reaction is related to the potassium level, and the sugar to the calcium), but it shows a distinct correlation with the skin reactions to epinephrine The wheal of the latter increases with increasing weight, and with lowered metabolic rate, the flare diminishes

If one wishes to use the term sympathetictonic or vagotonic, one can say that the heavy group is the parasympathetic group, and the thin group the sympathetictonic We do not, however, believe that these terms are justifiable or helpful, because there are too many divergent autonomic reactions (Table 6)

TABLE 6—*The Relation to Weight*

Heavy Persons		Thin Persons
Low	Permeability of the capillaries	High
High	Potassium	Low
High	K / Ca ratio	Low
Low	CO ₂	High
Low	Basal metabolic rate	High
Low	Skin resistance to electric current	High
Low	Muscle reactivity to electric current	High
Low	Reaction to epinephrine (pulse pressure)	High
Increased	Reaction to epinephrine, wheal	Diminished
Increased	Reaction to epinephrine, flare	Diminished
Diminished	Reaction to thyroxin, wheal	Increased
Diminished	Reaction to thyroxin, flare	Increased
Increased	Cholesterol	Decreased

The age of persons plays relatively little rôle in the reactivities that we have studied The blood pressure is, of course, increased and the inflammatory index is lowered, as is the permeability of the capillaries The reaction to ice, too, is somewhat delayed in old age

EXPLANATION OF TERMS USED

Blister Time—The time in hours for the formation of a blister on the forearm following the application of a cantharides plaster

Permeability of Capillaries—The ratio of the protein in the blister to the protein in the capillary blood

Albumin/Globulin Ratio—Method of Naegele

Krohmayer Erythema Time—The time in hours for the first appearance of erythema following a thirty-second exposure of the forearm to the Krohmayer lamp

Skin Resistance—The resistance of the skin of the forearm to the passage of a direct current of electricity

Muscle Reaction—Muscle reaction (CCC)

Epinephrine Reaction—The average percentage increase or decrease from the preinjection level of the pulse pressure for one hour after the injection

Epinephrine Reaction—The average percentage increase or decrease from the preinjection level of the pulse pressure times pulse rate for one hour after the injection

Ice Reaction—The time in seconds for the appearance of an erythema following a transient application of ice to the chest wall

Weight/Length Ratio—The weight in pounds divided by the length in inches

Intracutaneous Reactions to Pharmacologic Substances—The size of the wheal and of the flare (in mm) at the site of the intracutaneous injection of epinephrine hydrochloride 1 1,000,000, 1 100,000, 1 10,000 and 1 1,000, morphine 1 10,000,000 and 1 1,000,000, thyroxin 1 10,000 and caffeine 1 100

II THE CLINICAL STATUS OF THE GROUP OF ONE HUNDRED "NORMAL" MEN

In the first part of the study, we presented a table of possible correlations of certain reactions of the skin (the blister time, the reaction time to the Kromayer light, the reaction time to ice, the resistance of the skin to electric current, the reactions to intracutaneous injections of pharmacologic substances, etc.) with the blood chemistry.

In the present analysis of this material, we proceed to a grouping of the men into clinical subdivisions, based on the physical observations and on the results of the urinalyses, the examinations of the blood pressures, the Wassermann tests, the roentgenologic interpretations, the microscopic examinations of the capillaries of the skin, etc.

In arranging the individual results of the examinations of these men, we first present table 1, which classifies the men as follows: a normal group of 20 men (column 3), a group of 9 proved by the x-rays to have active tuberculosis (column 4), a group of 17 with healed parenchymal tuberculosis, as evidenced by the x-rays (column 5), a group of 4 with syphilis (column 6), a group of 40 with cardiovascular renal disease, which has been subdivided to include those with arteriosclerosis, as shown by the x-rays (column 7), those with probable myocarditis, as shown by the x-rays (column 8), those with an increased range of blood pressure (column 9), those with a normal range of blood pressure (column 10), those with a low range of blood pressure (column 11), those with changes in the urine—casts or albumin (column 12) and those with alterations of the capillaries of the skin—granulation, tortuosity, slowing, etc. (column 13), a sensitized group of 2 (column 15), a "nervous" group of 4 (column 16), and a group of 4 with miscellaneous conditions, making a total of 100 men.

The following tables have been prepared: Table 2 contains the results of the examinations of the normal men, table 3, of men with roentgen evidence of healed tuberculosis, and table 4, of men with roentgen evidence of active tuberculosis.

The cardiovascular renal material has been recorded in the following way: in table 5, the results of the examinations of men with increased blood pressure, but without urinary changes, in table 6, of men with increased blood pressure with urinary changes, in table 7, of men with normal blood pressure and normal urine, but with x-ray evidence of arteriosclerosis or myocarditis, in table 8, of men with normal blood pressure, but with urinary changes, in table 9, of men with blood pressure under 110 (including the syphilitic group, normal men and men with roentgenologic evidence of healed tuberculosis), and in table 10, of men with low blood pressure, but with urinary changes.

The averages for these groups have been brought together in table 11.

TABLE 1—Classification of One Hundred So-Called Normal Men on the Basis of the Results of Physical Examinations

Serial Number	Individual Number	Normal Persons	Cardiovascular Renal														Sensitized	Nervous	Miscellaneous
			Tuber- culosis, Shown by Roentgen ogram		Syphilis	Arteriosclerosis of Large Vessels (X Ray)	Myocarditis (X Ray)	Blood Pressure			Changes in Urine (Casts or Albumin)	Changes in Skin Capillaries	Cardiovascular Renal						
			Active	Healed				High	Normal	Low									
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17			
1	3			1															
2	4	1																	
3	8	1																	
4	10			1															
5	13			1															
6	14																		
7	15			1					+		+		1				(Liver)		
8	17	1																	
9	18			1															
10	20		1																
11	21			+				+				+	1						
12	23			1						+									
13	24			1															
14	25		1					+			+		+						
15	26				1					+									
16	28			1															
17	29	1																	
18	30					+		+					1						
19	32							+					1						
20	34			+					+			1							
21	35	1								+									
22	36									+	+		1	+			(Hay fever)		
23	37	1																	
24	39			+	1														
25	40			+								1							
26	41	1																	
27	42					+			+				1						
28	43	1								+									
29	44	1																	
30	45					+		+					1						
31	46							+				+	+			1	Inanition		
32	47			1															
33	48			+	1					+		+							
34	49								+		+		1						
35	50	1																	
36	52			1															
37	53	1																	
38	54					+			+	+	+		1	+					
39	55			+					+		+		1						
40	56		1											+					
41	59	1																	
42	61					+		+			+	+	1						
43	62							+					1				(Aortic regurgita tion)		
44	63			+		+			+				1						
45	64	1																	
46	65									+	+	+	1						
47	66					+	+		+		+	+	1						
48	67																1 Dwarf		
49	68			1															
50	70					+		+			+		1						
51	71					+			+				1						
52	72	1																	
53	73				1					+									
54	74											1							
55	75			+				+					1						
56	76					+			+		+		1						
57	77													1					
58	78	1																	
59	79			+		+		+				+	+			1	1 Ulcer		
60	80																		
61	81						+	+					1						
62	82							+				+	1						
63	83	1																	
64	84							+			+		1				(Angioneurotic edema)		
65	85															1	Elevated tempera ture (cause un known)		

TABLE 1—Classification of One Hundred So-Called Normal Men on the Basis of the Results of Physical Examinations—Continued

Serial Number	Individual Number	Normal Persons	Tuberculosis, Shown by Roentgenogram		Syphilis	Arteriosclerosis of Large Vessels (X Ray)	Myocarditis (X Ray)	Blood Pressure			Changes in Urine (Casts or Albumin)	Changes in Skin Capillaries	Cardiovascular Renal	Sensitized	Nervous	Miscellaneous
			Active	Healed				High	Normal	Low						
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
65	86															
67	87	1								+				+	1	
68	88		1													
69	89			1						+						
70	90														1	
71	91				+				+			+	1			
72	92									+					1	
73	93						+		+				1	+		
74	94	1														
75	95			1												
76	96					+		+					1			
77	97	1								+						
78	98					+			+				1			
79	99			1												
80	100			1												
81	101			+												
82	102		1													
83	103					+	+		+				1			
84	104		1			+		+					+			
85	105			1						+						
86	106					+			+				1			
87	107					+	+		+				1			
88	108		1							+		+	+			
89	110			1												
90	111			+		+			+				1			
91	112					+			+				1			
92	113			+		+			+				1			
93	114		1			+						+	+			
94	115			+				+				+	1			
95	122	1								+						
96	127			+						+		+	1			
97	128			+		+			+			+	1			
98	129		1									+	+			
99	130									+		+	1			
100	134					+		+				+	1			(Aneurysm)
		20	9	17	4							3	37	2	4	4

COMMENT

The Normal Group—In the normal group, there have been included men whose blood pressure is under 140, with no urinary changes, no roentgen evidence of tuberculosis and no alterations of the capillaries of the skin, with negative Wassermann reactions and without history of sensitization.

Even with such criteria, it is to be expected that certain ones may be abnormal in the sense that chronic pathologic conditions of the organs, either anatomic or functional, may exist, but need not be clinically apparent in one examination. Thus, a number of deviations are observed in the course of the examinations.

Blister Time The blister time is shortened only in patient 122, a young medical instructor, apparently normal, who gives a history of

TABLE 2—The Results of the Examinations of

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, M ₁	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate, per Cent
														Systolic	Diastolic			
4	6	62	95	118	212	18	943		828	2	+12	034		114	90	80	21	455
22	4	68	17	106	192	181	50	18	806	2	-7	037	24	102	50	63	-3	-6
29	65	70	107	10	239	239	76	1	828	325	+35	074	11	134	88	76	+24	+24
35	6	54	67	87	252	29	79	2	828	125	+123	035	2	108	78	62	+33	+47
41	6	55	91	98	212	216	70	1	849	125	+15	026	32	110	74	64	+23	+33
43	625	60	97	92	174	189	67	1	763	175	-44	027	35	96	50	74	+18	+40
44	8	56	7	10	176	176	90	2	849	175	-12	036	3	120	68	60	+7	+22
50	8	71	88	114	274	24		233	828	3	+21	048	2	128	70	67	+12	+20
64	65	66	10	9	166	184	52	35	741	3	+23	022	5	113	59	64	+15	+18
72	6	63	115	108	187	173	72	28	773	2	+159	027	36	114	76	54	+23	+46
78	7	86	12	84	188	223	67	15	849	325	-62	062	1	122	70	74	+11	+20
83	9	51	56	82	19	231	63	15	773	15	-7	016	4	118	64	58	+96	+9
87	6	56	93	84	195	232	94	23	755	15	+18	042	4	102	58	69	+40	+53
97	6	54	9	84	209	237	60	14	785	175	+25	022	45	100	63	68	+20	+30
17	8	66	82	127	182	143	615	5	872	15	-11	022	6	130	70	66	0	0
53	8	62	77		228		77	3	806	15	+318	035	67	125	73	80	+32	+32
59	6	52	86	96	188	195	85	5	785	15	-65	016	4	116	69	74	+2	+8
8	7	75	107	105	21	2	73	212	806	115	-8		32	120	86	64	+90	+120
37	9	56	62	10	226	226	75	14	785	15	-24	034	3	116	70	84	-8	-6
94	6	53	88	84	175	208	75	17	785	145	-18	043		134	78	53	+20	+50
	68	62	93	97	203	21	728	222	804	183	+5	033	37	116	70	68	+196	+236

TABLE 3—The Results of the Examinations of the Men who Were

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, M ₁	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate, per Cent
														Systolic	Diastolic			
95	6	59	98	78	188	241	77	23	85	185	+26	039	16	110	66	68	+9	+17
3	65	67	111	111	163	147	733	186	741	15	-65	033		114	65	76	+8	+26
13	8	64	8	96	238	248	78	4	77	25	-22	089	27	132	84	72	24	37
15	9	68	75	121	188	155	704	4	795	15	-49	019	6	128	63	60	+13	+20
23	6	67	111	131	286	219	85	4	787	175	+109	042	3	102	58	82	+25	+41
21	6	70	116	117	248	212	81		720	2	+1	019	2	110	58	78	+50	+62
52	8	61	76	104	209	2	66	4	785	15	+05	044	1	110	61	75	0	+4
00	6	53	9	9	215	238	72	12	785	1	-16	011	38	128	58	76	+8	+13
10	75	64	72	121	163	134	61	25	720	4	+48	060	2	114	60	86	-4	-4
68	7	78	11	88	171	194	68	23	866	15	+258	053	5	138	76	89	+31	+36
89	6	52	86	92	167	181	75	2	751	125	+25	016	16	100	60	73	0	+2
99	9	77	81	95	179	186	71	4	785	45	-3	014	42	116	78	70	+12	+24
05	9	62	7	9	171	181	52	16	763	25	+316	009		108	70	82	+26	+26
18	8	70	87	145	212	146	702	18	830	325	+42	100	2	120	80	88	10	
28	6	64	106	11	241	219	72	14	763	175	+245	008	4	118	76	65	+21	+32
10	6	64	133	101	246	24	74	212	870	25	-12	042	36	120	70	70	0	0
47	5	62	128	104	262	251	72	15	838	145	+34	013	5	136	64	70	-5	+10
	73	648	96	105	208	198	716	243	788	215	+8	036	297	117	67	75	134	20

the Men Who Were Grouped as 'Normal'

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffien, Wheel (Diameter, Mm)	Caffien, Flare (Radius, Mm)
64	Sthenic	-	+	Normal		40	237		22 8	10 6	16	17	10 2	0	10 2	0
56 8	Asthenic			Normal		33	189	209	20	7 8	10	6 6	12	9	21 2	0
60 1	Sthenic		+	Normal	15	13	214		26 8	9 4	14	12 2	7 2	0	5	0
57 6	Sthenic		+	Normal	20	44	203		22 8	11	14 8	20 4	9 2	0	5 2	0
58 6	Asthenic		0	Normal	7	40	216		21	7 2	13 8	18 8	6 2	0	5 8	0
60 1	Asthenic		0	Decreased in quantity	7	45	231		22	7 4	11 2	20 6	10	0	11	0
57 1	Sthenic		0	Normal	20	48	214		10 6	9 4	12 8	15	10 2	3 8	15	4 4
64 9				Normal	15	20	237		21 8	10 6	9 8	15 4	10 4	10	14	0
55	Sthenic			Normal	7	31	208	180	20	10 6	13	15	12 2	10 8	16 2	0
60 6	Sthenic		+	Normal	20	42	230		18	12 1	15 6	17 8	15 4	6 6	20 2	15 4
62 6	Asthenic			Normal	10	33	203		19 6	12	9 4	20 4	12 4	6 2	20 2	7 4
53 1	Sthenic			Normal	20	43	258		17 2	9 2	9 2	20 8	13 4	11	21 4	10 2
55 4	Sthenic			Normal	18	16	200		16	8 8	10	12 4	12	5 4	25 4	10 2
57 2	Sthenic		+	Slight dilatation	20	53	230		19 2	9	8 8	16 4	12	9	33	0
59 1	Normal		0	Normal	20	23	216		22 6	10 2	12 4	7	20 6	10 4	30 4	2 6
53 9	Sthenic	-		Normal	10	39	231		17 2	11 8	10 4	26 4	12 2	11 2	23	6
56 6	Sthenic	-		Normal	10	37	252		23 6	7 2	9 2	21 4	15 6	8	23 4	6
56 1	Asthenic	-	+	Normal	17	38	200		20 4	9 6	13 2	13 4	14 4	0	19	0
52	Sthenic	-	+	Normal	20	45	254		22 6	7	10 2	15 2	6	0	8 4	0
51 5	Sthenic	-		Normal	15	57	236	303	20	6	11 2	14	11 2	7 8	30 6	0
57 6					14 5	40 2	224	222	21	9 36	11 7	16 3	11 6	5 45	17 9	3

Grouped as Having Roentgenographic Evidence of Healed Tuberculosis

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffien, Wheel (Diameter, Mm)	Caffien, Flare (Radius, Mm)
61 6	Sthenic	Healed	+	Normal	10	54	222	318	23 6	6 4	10 2	12 6	12	6 2	26 2	
68 6	Asthenic	Healed	+	Normal	14	25	224	243	19 4	12 2	12 4	18 2	6 4	9 2	4 8	
67 6	Sthenic	Healed	+	Normal	15	53	223	185	13 2	6 8	12 4	11 2	22 6	9 2	25 6	
57 4	Sthenic	Healed	0	Normal	33	60	210		23 2	12 6	11 2	12 4	11 6	12	12 4	10
53 7	Sthenic	Healed	+	Normal	23	54	233		17 2	8 2	10 6	17 8	9 2	3 2	7 2	4
52 9	Sthenic	Healed		Normal	20	30	219		16 8	12	9	27 2	6 6		7 2	
53 3	Sthenic	Healed		Normal	15	36	213		17 6	10	12 8	19 2	11 2	12 4	20	7 8
57 2	Asthenic	Healed		Decreased	5	45	241	208	18 8	8 6	11 4	10 6	12	9 2	27 6	
51 1	Asthenic	Healed		Normal	30	62	190	222	21 8	4 2	9 6	14 6	12	9 4	18 2	
56 3	Asthenic	Healed		Normal	10	35	217	238	18	9 6	12 4	10 2	12	11	22 4	1
57 4	Sthenic	Healed		Normal	16	41	204	222	20 8	9 8	9 2	20	10 2		20 4	
64 4	Asthenic	Healed	?	Normal	11	46	228	230	20 4	7	12 2	11 2	12 2	9 2	29 4	
58 4	Asthenic	Healed	0	Normal	13	56	194	233	19 6	5 6	9 2	16	12	10 4	27 2	
66	Asthenic	Healed	+	Normal	10	31	200				6 6	22 6				
60 4	Sthenic	Healed	0	Normal	25	43	200		20	12 2	10 8	15 2	7 4		7 2	
56 4	Sthenic	Healed	+	Normal	7	40	230		20	8 4	12 6	14 6	9	7 2	12 2	
57 9					16 5	43 6	218	233	19 2	8 66	11	15 5	11	6 2	17	1 5

TABLE 4—The Results of the Examinations of the Men Grouped

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Oa Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, Ma	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate per Cent
20	6	64	10.6	11.4	17.4	1.53	85	1.70	8.28	1.5	+20.4	0.25	5		130	76	80	+13	+28
25	6	57	9.5	11.1	28.8	2.60	67	0.43	8.50	1.75	+2	0.24	1.2	+	140	80	86	+35	+44
56	6	61	10	9.8	28.6	2.52	65	1.6	9.13	2.15	+17.9	0.32	1.1		124	88	79	+14	+22
104	9	54	6	7.4	22.9	3.09	55	1.2	7.51	1.75	+27.5	0.08	1.2		176	100	84	+11	+11
114	8.5	64	6	8	19.2	2.4	75	2.3	8.06	2.25	+11.2	0.12	4	Albumin, blood +	174	60	48	+6	+60
129	15	52	3.5	8.9	19	2.13	83	1.3	7.85	2.5	+28	0.22	2.2		116	66	92	10	13
108	8	63	8	10.4	15.3	1.47	63	1	7.85	1.75	+17	0.44	0.6		94	62	71	+9	+29
102	11	64	5.8	10.6	17.3	1.63	62	0.82	7.95	1.5	+22	0.20	2.4		114	60	96	+11	+5
88	7.25	58	8	9.4	13.1	1.4	79	2	7.63	2		0.68	2.5		128	76	76	-10	0
	8.4	59	7.5	9.6	20.1	2.08	70	1.4	8.08	1.9	18.2	0.28	2.2		133	73	78	+11	+23

TABLE 5—The Results of the Examinations of the Men in the Cardiovascular

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Oa Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, Ma	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate per Cent
46	6	59	10	13.8	17.4	1.24	61	2.3	7.63	1.15	+13	1.7	2	140	82	76	+15	+37
21	7	62	9	10.2	25.6	2.51	72	4	8.06	1.75	+4.3	0.74	3.9	140	80	72	0	-8
32	6	60	10	9.5	26.1	2.75	76	2.3	8.80	1.75	+22	1.18	7.4	144	86	74	+22	+30
45	6	54	9	11.2	16.6	1.48	77	1.5	7.73	0.75	+20	0.28	7.4	162	114	84	-3	+8
79	15	86	5.7	11.2	20	1.78	67	1	8.78	4	-15.2	0.71	7.7	140	80	60	+8	+10
81	6	59	10	8.4	25.8	3.07	63	1.7	8.49	1.5	+35	0.10	2.3	144	54	76	+4	+4
75	9	60	6.6	10.8	19.2	1.78	75	1.6	9.23	3	+2.5	1.3	5	146	80	77	-9	-15
82	6	58	9.6	11.4	17.2	1.5	58	2	7.41	1.5	+7	0.20	5.7	170	100	61	+31	+37
30	6	55	9.1	10.3	24	2.33	76		7.07	1.5	-5.9	1.05	1.8	150	72	85	0	-10
96	8.25	57	7	8.2	17	2.02	77	1.8	7.26	1.75	+31	0.11	2.6	140	85	68	+25	+28
	7.5	61	8.6	10.47	20.8	2	70.2	1.82	8.04	1.86	11.4	0.7	4.6	147	83	73	9.3	14.1

as Having Roentgenographic Evidence of Active Tuberculosis

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare
62.3		Asthenic	++++	0	Normal	10-20	42	226		21.2	6.6	12.4	15.4	10	2.6	9	0
59.8		Asthenic	++++		Normal	20	35	183		21.4	12.2	8.2	17.8	9	15.2	10	6.2
56.5		Sthenic	++++		Normal	15	44	247		17.2	5.8	10.8	22.4	14	7	21.4	7.2
57.2	+	Dilatation of aorta, arteriosclerosis	++++		Normal	25	76	235	230	20.8	6.2	10.8	10	12	0	15.2	0
60.6		Sthenic	Left upper bronchus	+	Normal	25	79	235	208	20	7.2	10.2	10.2	12	9	22.2	0
61.1		Sthenic	+	+	Granulations	17	66	247	235	18.4	7	10.6	9.6	12.2	0	13.2	0
54.1		Asthenic	Hilum bronchi		Slight granulations	18	67	196	189	18	2.4	10.2	11	14.8	13.2	23.4	3.4
60.9	+	Asthenic	+	+	Normal	40	65	170	208	23.2	7.4	10.8	15	12.2	0	18.2	7
58.1		Asthenic	++++		Normal	15	55	203	230	18.4	11	11.6	20	12.4	12	27.6	0
58.8						21	58.7	215	208	20	7.2	10.6	14.6	12	6.4	18	2.6

Renal Group Having Increased Blood Pressure but No Urinary Changes

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare
56.2		Asthenic		+	Sluggish, empty	15	29	168		21.2	13.2	15.0	16.2	12.2	11.2	25.2	9.2
62.9		Asthenic	Healed	0	Dilated, in granulations	25	56	200		23.2	12.6	8.8	13.2	7.2	2.6	5.2	
54.1		Sthenic		0	Normal	23	26	190		23.6	11.2	11	21.4	9.8		8.4	
54.3		Sthenic, myocarditis		0	Normal	20	40	317		20.4	9.8	14.2	21.4	16.4	12	20	4.8
57	+	Arterio sclerosis	Healed		Normal	20	58	220	230	19.2	9.4	10.2	17.8	8.2	12.2	30.6	5
57		Myocarditis		+	Normal	45	63	209	222	14	6.2	10.2	15	10		16.4	9.6
61.6		Sthenic	Healed	+	Normal	10	54	243	278	20.4	10.2	18	15.2	10		23.4	8
58.8		Sthenic		1890	Slightly tortuous	25	66	208	190	21.2	7	14.2	14.2	11		27.6	9
62	+	Arterio sclerosis		0	Normal	15	42	175		20	8.8	8.2	16	7.2		7.2	
53.4		Arterio-sclerosis		+	Normal	40	70	245	167	18	8.2	11.4	15.4	12.4		28.4	
57.7						24	50.9	217.5	217	20.1	9.72	12	16.6	10.4	3.8	19.2	4.6

TABLE 6—*The Results of the Examinations of the Men in the Cardiovascular*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, Ma	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine Pulse Pressure x Pulse Rate per Cent
															Systolic	Diastolic			
51	6	10	11.6	7.6	17.9	2.35	72	3.5	7.41	1.75	+0.9	0.28	7.4	+	142	82	64	+8	+17
70	10.5	74	7	11.4	16.6	1.45	67	1.9	8.65	1.25	+23	0.39	4	++	148	50	76	-6	+2
1	11	71	6.4	10	17.8	1.78	67	1	7.85	1.5	-5	0.28	2.8	+	140	78	80	+6	+3
15	8	46	5.7	7.8	15.2	1.95	60	0.66	8.28	1.65	+15	0.28	2	Albumin, sugar + Casts	148	84	84	-4	-4
4	15	60	4	9.9	15.4	1.56	71	1.4	7.85	1.35	-4	0.7			116	86	78	0	+5
	10.1	64	7	9.34	16.6	1.82	67	1.7	8	1.5	6	0.38	4		145	76	76	0	+4.6

TABLE 7—*The Results of the Examination of the Men in the Cardiovascular Renal Group with Normal*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, Ma	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine Pulse Pressure x Pulse Rate per Cent
														Systolic	Diastolic			
2	7.25	47	6.5	11.4	17.8	1.56	71	1	7.68	2	+6.8	0.15	4.5	136	70	86	0	+19
3	6.5	60	9.2	10.2	18.6	1.82	66	1.5	7.41	1.75	-6.2	0.34	3.2	136	72	60	+8	+8
1	6	70	11.6	8.8	17.5	2	73	2.3	8.5	1.1	+7.4	0.36	1.4	114	70	88	+18	+18
3	6	50	8.3	7.6	24.5	3.2	70	1.4	8.59	1.45	0	0.25	2.4	114	71	88	+19	+19
3	6	52	8.6	9.2	17.3	1.88	57	1.5	7.73	1.75	+2	0.39	1.4	126	70	76	1	+6
6	6	71	12	11.2	19	1.69	65	1.7	8.06	1.45	-6	0.63	2.2	120	80	84	-5	-1
7	9	58	6.4	8	18.1	2.3	60	1.5	8.06	4.75	-6.5	0.33	2.8	134	72	72	-1	+2
1	6	37	9.5	11.8	18.3	1.5	75	1.5	8.23	1.15	+31	0.33	1.2	122	70	92	+19	+21
2	6	54	9	12.6	18	1.42	68	2.1	7.44	1.15	+19.6	2.7	2.4	139	80	75	+5	+14
3	8.25	57	7	8.2	17	2.07	77	1.85	7.11	1.75	+31	0.11	2.6	140	85	68	+25	+28
1	7	56	8				67	2	7.85	2.5	-1.7	0.30	4	136	64	76	+26	+34
38	7.5	71	9.4	11.4	20.9	1.82	62	1.5	7.68	5	+0.65	1.4	5	116	62	60	+5	+35
	6.8	58.5	8.7	10	18.6	1.86	67	1.65	7.90	2.15	6.5	0.60	2.67	127	72	77	+9.8	17

Renal Group Having Increased Blood Pressure with Urinary Changes

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare
53.1		Arteriosclerosis			Slight granulation	7	51	208	2.7	10.6	9	14.4	17.6	13.4	0	20.2	5
56	+	Arteriosclerosis, dilated aorta			Normal	45	65	264	222	18	11	9.8	18.2	10	0	24.6	~
53.1		Asthenic			Normal	20	73	200	167	16.4	8.4	8.2	19.2	10.2	7.2	20.6	0
51.8		Sthenic	Healed	+	Normal	10	66	215	247	18.2	6.2	11	13.2	14.2	8	16	9
54.8		Arteriosclerosis		+	Normal	12	67	233	196	23.6	17.8	11.4	13.2	19.2	9.6	28.6	3
53.7						19	64.5	224	220	19	8.9	11	16.4	13.4	5	22	5

Blood Pressure and Normal Urine but with X-Ray Evidence of Arteriosclerosis or Myocarditis

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare (Radius, Mm)
54.5		Myocarditis		0	Normal	32	33	241		19.2	11.8	10.8	16.8	9.2	4.6	6.8	0
62.7	++	Arteriosclerosis	Healed		Normal	12	59	213	222	18.4	9.2	9.6	18.8	10.6	10.6	18.2	0
57.9		Arteriosclerosis			Normal	15	42	195	256	19.2	9.6	12.6	18.2	15.4	11	24.4	8.2
57	++	Myocarditis			Normal	12	53	267	230	20.4	8.6	12.4	15	10	0	22.4	0
55.3	+	Arteriosclerosis, myocarditis			Normal	5	59	270	215	22.4	9	12.2	18.2	12.2	0	18.2	0
49.5	+	Aorta, arteriosclerosis			Normal	30	60	243	222	19.6	7	9.2	14.4	11.2	0	25.6	0
55.2	+	Myocarditis		+	Normal	15	62	265	256	20.8	5.8	8.6	11.2	13.4	6.2	21.4	0
55.3	++	Arteriosclerosis	++	++	Normal	15	60	200	290	22	9.4	11	15	10.8	5.6	25.2	0
59		Arteriosclerosis	+	+	Normal	18	60	218	215	22.4	7.2	10.8	18.4	9.6	0	24	0
53.4		Arteriosclerosis		+	Normal	40	70	245	167	18	8.2	11.4	15.2	12.4	0	28.4	0
58.9	+	Arteriosclerosis			Venous capillaries tortuous	45	66	208	222	16.8	6.8	8.8	16.6	12	9.4	22	0
62.4		Arteriosclerosis	Healed			17	40	190	215	20	11	17.2	15.2	12.2	0	26.2	0
55.9						21	55.3	229	228	20	8.62	11.2	16.1	11.6	4	21.8	0.6

TABLE 8—The Results of the Examinations of the Men in the Cardiovascular

	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, M ₂	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate, per Cent
															Systole	Diastole			
14	7	71	10.5	11.2	19.6	1.75	67	1.7	8.06	1.55	-27	0.20	21	Cast, sugar	128	80	76	0	0
15	8.5	60	7	8	21.9	3.1	73	1.5	7.75	2.75	+6.2	0.33	0.6	+	128	68	84	+5	+8
16	6	78	13	11	20	1.82	67	1.22	8.66	0.85	+1.3	0.37	3.5	+	123	66	77	+37	+44
18	15	68	3.8	9.4	19.7	2.09	79	0.8	8.06	4	-18	1	0.6	+++	122	80	84	+13	+24
19	6	66	11	11	23.2	2.29	74	4.8	8.23	5.5	+7.2	0.32	2	+	134	72	60	+21	+41
	8.5	67	9	10.1	21.9	2.2	72	1.14	8.16	2.93	0	0.45	1.76		128	73	76	+15	+23

TABLE 9—The Results of the Examinations of the Men in the Cardiovascular Renal Group and Those with Roentgenographic

	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Wassermann Reaction	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, M ₂	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure x Pulse Rate, per Cent
															Systole	Diastole			
26	6.5	72	11	10.2	26.6	2.61	69	1.9	8.28	Slight	1.25	+9.6	0.38	2	92	48	68	+12	+6
27	6.5	66	9.7	9.6	27.6	2.87	71	1.5	8.59	Slight	1.23	+8.5	0.10	1.6	104	72	84	+9	+12
28	9	66	7.6	11.2	19.5	1.74	71	2.3	8.5	Slight	2.1	+16.3	0.20	3	104	70	51	+3	+10
29	6	67	11.1	13.1	28.6	2.19	75	2	7.87		1.75	+10.9	0.42	3	102	58	82	+25	+41
30	6	52	8.6	16.7	17.1	1.81	75	2	7.51		1.25	+25	0.16	1.6	100	60	73	0	+3
31	6	52	7.7	9	17.1	1.81	52	1.6	7.63		2.5	+31.6	0.09		108	70	82	+26	+26
32	6	56	9.3	8.4	19.5	2.32	94	2.3	7.55		1.5	+18	0.42	4	102	53	69	+40	+53
33	6	54	9	8.1	20.9	2.37	66	1.4	7.85		1.75	+29	0.22	4.5	100	63	68	+20	+30
34	4	68	17	10.6	19.2	1.81	50	1.8	8.06	?	?	-7	0.37	2.4	102	50	68	-3	-6
35	6.25	60	9.7	9.2	17.4	1.89	67	1	7.63		1.75	-4.4	0.27	3.5	96	50	74	+18	+40
36	8	54	6.7	8.7	25.2	2.9	79	2	8.28		1.25	+12.3	0.38	2	108	78	62	+33	+47
	6.7	61	9.3	9	19.8	2.2	70.8	1.78	8		1.73	+13	0.26	2.76	101	61	71	+16	+23

Renal Group Having Normal Blood Pressure with Changes in the Urine

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffem, Wheel (Diameter, Mm)	Caffem, Flare (Radius, Mm)
65		Asthenic	0	0	Normal	40	36	198	278	24.4	6.2	13.2	7.2	15	4.4	9.8	10
56.6		Asthenic	Healed	+	Normal	20	50	170		17.6	8.2	10.2	19.6	11.2		12.2	
53.1	+	Arteriosclerosis, myocarditis		—?	Tortuous, beaded	30	64	257	215	20	9.2	13.6	16.6	10.2		18.2	
58.1		Arteriosclerosis	Healed		Slight granulation	24	66	180	230			12.6	10.2	14.4		22.6	
59.1		Sthenic			Normal	15	42	239		18.4	10.2	13	12.2	4.2	1	9	
58.4						26	51.6	209	241	20	8.2	12.4	12.6	11	1	14.4	2

with Blood Pressure Under 110 (Including the Syphilitic Group, the Normal Group, Evidence of Healed Tuberculosis)

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffem, Wheel (Diameter, Mm)	Caffem, Flare (Radius, Mm)
63.4	Sthenic		0	Normal	35	30	210		19.6	10	10	8.6	7.2	6.4	10.4	0
58	Sthenic	Healed	0	Tortuous	35	46	222		19.2	8.4	15.2	12	8	0	7	0
59.7	Asthenic			Normal	35	48	191	247	17.6	8.2	12	16	15.6	0	2	8
57.9	Sthenic	Healed	0	Normal	28	54	233		17.2	8.2	10.6	17.2	9.2	3.2	7.2	6
56.3	Asthenic	Healed	+	Normal	16	41	204	222	20.8	9.6	9.2	20	10.2	0	20.4	0
64.4	Asthenic	Healed	?	Normal	15	56	194	238	19.6	5.6	9.2	16	12	10.4	27.2	0
55.4	Sthenic			Normal	18	46	200	222	16	8.8	10	12.4	12	5.4	25.4	10.2
57.2	Sthenic		+	Dilated, U-shaped	20	53	230	245	18.2	9	9.8	16.4	12	9	32.6	0
56.8	Asthenic			Normal	5	33	189	209	20	7.8	10	6.6	12	9	21.2	0
60.1	Asthenic			Decreased	7	45	231		22	7.5	11.2	20.6	10	0	11	0
57.6	Sthenic		+	Normal	20	44	203		22.8	11	14.8	20.4	9.2	0	5.2	0
58.7					21	45.1	209	230	19.44	8.5	11	15.2	10.6	3.94	14.2	2

TABLE 10—*The Results of the Examinations of the Men in the Cardiovascular*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, Ma	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine Pulse Pressure x Pulse Rate per Cent
															Systolic	Diastolic			
36	8	58	72	121	263	217	90	2	828	2	+13	011	36	+	104	50	84	+22	+28
130	15	71	47	95	155	163	86	066	799	2	+12	035		+++	106		64		
54	6	60	10		22		80	2	828	125	-34	026	26	+	104	80	68	+66	+90
65	6	61	10	98	164	167	65	17	828	3	+29	035	01	++	100	70	68	+30	+42
76	85	76	9	108	202	187	77	23	82	165	+8	028	96	+	108	82	67	+11	+8
127	13	50	38	97	162	167	81	2	785	425	-35	12	3	+++	108	74	88	+60	+54
	97	59	74	104	194	186	80	177	814	236	72	051	39		105	71	72	+38	+44

TABLE 11—*Averages of the Results of the Individual*

	Number in Group	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Protein, Mg	Wassermann Reaction	Kromayer Light Erythema Time, Hr	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, Ma	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent
																	Systolic	Diastolic		
Table 2 Normal group	20	68	62	93	97	203	21	728	222	804		183	+5	033	37		116	70	68	+190
Table 3 Normal group with x-ray evidence of healed tuberculosis	17	73	648	96	105	208	198	716	243	788		215	+8	036	3		117	67	75	134
Tables 2 and 3 Average normal group	37	7	633	94	101	206	204	723	232	796		197	+63	035	35		116	69	71	+160
Table 4 Roentgenographic evidence of active tuberculosis	9	84	59	75	96	201	208	70	14	808		19	+182	028	22	3/9	133	73	78	+11
Table 5 Increased blood pressure, urine normal	10	75	61	86	1047	208	2	70	182	804		186	+114	07	46	0	147	83	73	+93
Table 6 Increased blood pressure, urine +	5	101	64	64	934	166	182	67	17	8		15	+6	038	4	5/5	145	76	76	0
Table 7 Normal blood pressure, normal urine, x-ray evidence of arteriosclerosis or myocarditis	12	68	585	87	10	186	186	67	165	790		215	+65	060	267	0	127	72	77	+98
Table 8 Normal blood pressure, urine +, arteriosclerosis or myocarditis	5	85	67	9	101	219	22	72	114	816		293	0	045	176	5/5	128	73	76	+15
Table 9 Low blood pressure, normal urine	11	67	61	93	9	198	22	708	178	8	3/11	173	+13	026	276	0	101	61	71	+16
Table 10 Low blood pressure, urine +	6	97	59	74	104	194	186	80	177	814		236	+72	051	39	6/6	105	71	72	+38

Renal Group Having Low Blood Pressure, with Changes in the Urine

CO ₂ Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Retention Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare
57.6	Asthenic		0	Normal	20	43	222		20.8	14.2	11.2	18	7.4	0	7.4	
55.5	Aneurysm sthenic			Normal	15	65	196	196	20	5.4	10.8	12.6	11.2	0	22.6	
56.6	Myocarditic en- rhosis of liver, sthenic			Normal	25	49	256	185	21.2	10.4	11	18	12	0	11.0	
53.1	Sthenic			Tortuous	12	34	221		14.8	13	12	19.8	9.2	10.2	10.4	
57.9	Arteriosclerosis, dilated aorta			Normal	10	43	230	215	20	6.6	12.4	19.6	11	7	12	
59.1	Asthenic	Healed		Normal	16	65	180	247	18.4	9.4	12	10.2	15.4	12	22	
56.6					16	49.8	218	211	19.2	9.8	11.8	16.4	11	4.8	14.2	

Examinations Set Forth in Tables 2 to 10

Epinephrine, Pulse Pressure x Pulse Rate, per Cent	CO ₂ Combining Power	Tuberculosis	Influenza	Capillaries	Ice Retention Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare (Radius, Mm)	Clinical Diagnosis and X-Ray Diagnosis
+28.6	57.6		7/20		14.5	40.2	224	222	21	9.36	11.7	16.3	11.6	5.45	17.9	3.1	
20	58.5	Healed parenchymal	6/17		16.5	43.6	218	233	19.2	8.66	11	15.5	11	6.2	17	1.5	Healed parenchymal tubercul
+24	58		13/37		15.6	41.8	221	228	20	9	11.3	16	11.3	5.8	17.4	2.38	
+23	58.8	Active (roentgeno-gram)	3/9	2/7	21	58.7	215	208	20	7.2	10.6	15.6	12	6.4	18	2.6	Active parenchymal tubercul
+14.1	57.7		2/10	3/10	24	50.9	217	217	20.1	9.7	12	16.6	10.4	3.8	19.2	4.6	Arteriosclerosis or myocardi (5/10 x-ray)
+4	58.7		2/5	1/5	19	64.5	224	220	19	8.9	11	16.4	13.4	5	22	5	Arteriosclerosis or dilated ac (3/5 x-ray)
+17	55.9		4/12	1/12	21	55.3	229	228	20	8.62	11.2	16.1	11.6	4	21.8	0.68	Arteriosclerosis or myocardit
+23	58.4		1/5	2/5	26	51.6	209	241	20	8.2	12.4	12.6	11	1	14.4	2	Arteriosclerosis
+23	58.7		3/11	1/11	21	45.1	209	230	19.5	8.5	11	15.2	10.6	3.94	14.2	2	
+44	56.6		1/6	16	49.8	218	211	19.2	9.8	11.8	16.4	11	4.8	14.2	0		

feeling tired. The blood sugar level and the blood pressure are low, the reaction to epinephrine is vagotonic and the weight/length ratio is low.

Permeability of the Capillaries High permeability occurs in only one man (no 78). The history is negative other than that the man has recently had an acute attack of rheumatism.

K/Ca Ratio A low ratio (1.43) is found in patient 17, a young laboratory technician. He has a markedly vagotonic reaction to epinephrine and shows other abnormalities. A high ratio occurs in patient 35, who is apparently normal.

Kromayer Lamp Erythema Time Two persons (nos 29 and 78) have prolonged Kromayer light erythema time. These men have high resistance of the skin to electric current and increased muscular irritability, as well.¹

The averages for this group of selected normal men, as compared with the averages for the entire series of 100, differ in the rapidity of the responses to cantharides, to Kromayer light and to ice, and in the lower resistance of the skin to electric current, and lower systolic blood pressure and pulse rate and the more marked reaction to epinephrine. The men are somewhat younger. Of the reactions to pharmacologic substances the wheal due to epinephrine is increased.

Healed Tuberculosis—The group of men with roentgenologic evidence of healed parenchymal tuberculosis are slightly older. The group averages slightly higher in cholesterol, and somewhat lower in serum proteins. The Kromayer light erythema time is increased twenty minutes. The muscle irritability seems somewhat greater than for the normal group. The pulse rate is increased. The men are somewhat thinner. The intracutaneous skin reactions other than the reduction of the wheal and flare due to epinephrine show no marked deviations.

Active Tuberculosis—When we turn to the group of men with x-ray evidence of active parenchymal lesions, several important differences make their appearance. It is probable that some of the differences are due to the increased age of the group and the associated cardiovascular renal disturbances. It should be emphasized that these men are ordinary workmen and there was no particular reason to suspect activity. The majority of the cases are undoubtedly chronic in a marked degree.

It will be noted that the blister time is longer, the permeability of the capillaries is low and, consequently, the inflammatory index is low,

1 Despite inclusion in this true "normal" group, we are inclined to consider patients 17, 29, 78 and 122 as abnormal because of their repeated deviations from apparently normal ranges for many of the tests. It was later found that patient 29 had bile in the urine.

and that the basal metabolic rate is distinctly increased, as are the muscle reactivity, the pulse rate and the ice reaction time. On closer examination (the section on the K/Ca ratio may be consulted here), it will be observed that the men can be grouped on the basis of the K/Ca ratio into those with low ratios and those with high ratios. Those with high ratios include the men with cardiovascular disturbances. Roentgenologic examination indicates that those with low ratios have asthenic hearts (all with low or normal blood pressure). Those with high ratios have sthenic hearts. Those with low K/Ca ratios have shorter reactions to the Kromayer light, lower blood pressure, lessened muscular irritability and diminished weight.

Cardiovascular Renal Groups—If we average the cardiovascular renal group and compare it with the normal, it will be noted that the blister time is longer, the globulins considerably increased, the Kromayer light erythema time prolonged, the resistance of the skin increased, the CO_2 combining power diminished and the ice reaction prolonged. Some of these differences must, of course, be attributed to the advanced age of the men. If we contrast the men having positive urinary conditions in the cardiovascular renal group with those having no urinary changes, we find that the blister time is longer and the capillaries appear to be somewhat more permeable. There is more globulin and the resistance of the skin to electric current is lowered.

If we compare the groups having increased blood pressure (5 and 6) with the groups having normal blood pressure (7 and 8), the following differences make their appearance. The blister time in the groups with increased blood pressure is prolonged, the Kromayer lamp erythema time shortened, the basal metabolic rate heightened, the muscular irritability lessened and the vascular reaction to epinephrine diminished.

III DETAILED STUDY OF THE "NORMAL" GROUP AND OF MISCELLANEOUS CLINICAL PATIENTS

In this part of the paper, we present the results of the clinical response to each of the various tests that we have carried out. The material consists of the 100 so-called normal men, as well as a considerable number of persons with diseases, chiefly exophthalmic goiter, glaucoma, diseases of the skin and certain vascular diseases (Raynaud's, Buerger's, etc.)

In table 1, the identification number, age, sex, occupation, nationality and clinical diagnosis of each person are presented. The identification numbers marked with an asterisk indicate persons included in the group of 100 so-called normal men.

METHOD OF PRESENTATION OF RESULTS

Since many different tests were made on each person, we proceeded to study each reaction separately, and to permit a rapid survey of the results, we adopted the following method. Results of each test for the entire group were arranged in numerical progression. A chart was made of this curve, and at the bottom of the chart we indicated the location on the curve and the clinical classification of the individuals of the group of 100 "normal" men. At the top of each chart, we usually indicated the location and clinical classification of the patients, particularly those with exophthalmic goiter and those with glaucoma. In addition to this chart, we made a tabulation of the twenty persons at each of the extreme ends of the curve and endeavored to correlate the results of other tests with the results of the one under consideration.

As the charts were all prepared in a uniform manner the first one—the chart of the blister time—is explained in some detail.

BLISTER TIME

When one analyzes chart 1, a number of features immediately present themselves. There appear to be proportionately more persons with roentgenologic evidence of healed tuberculosis in the region of the prolonged blister time with the cantharides method. The persons with roentgenologic evidence of active tuberculosis also tend to have a longer blister time. There are more of the persons showing cardiovascular renal changes in this end of the curve. This seems to apply not only to the group with urinary changes but to those with changes in the capillaries of the skin. Advancing age, increasing blister time and more frequent cardiovascular renal injury are obviously associated. The patients with glaucoma, as might be anticipated, are at the end of

TABLE 1—General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation

Individual No	Sex	Age	Nationality	Occupation	Clinical Notes
1	M	23	Jewish	Student	Out of school because of "nervous breakdown"
2	M	13	American	Schoolboy	Epilepsy and vasoneurosis
3*	M	25	Jewish	Instructor	Nervous, healed tuberculosis, father has Raynaud's disease
4*	M	40	American	Instructor	Normal
5	F	48	Jewish	Housewife	Nervous, cardiovascular renal condition healed tuberculosis
6	M	49	Jewish	Painter	Arteriosclerosis and myocarditis, syphilis, died
7	M	25	American	Student	Gastric ulcer, mother died of exophthalmic goiter
8*	M	33	German	Instructor	Normal
9	M	27	American		Exophthalmic goiter
10*	M	40	Norwegian	Technician	Healed tuberculosis
11	M	16	German		Exophthalmic goiter
12	M	40	Bohemian	Painter	Traumatic atrophy of muscle
13*	M	53	American	Janitor	Healed tuberculosis
14*	M	36	German	Technician	Probably gallbladder disease, cardiovascular renal condition
15*	M	60	American	Technician	Healed tuberculosis
16	M	33	American		Exophthalmic goiter
17*	M	28	German	Student	Normal, but with marked deviations in many tests
18*	M	31	German	Carpenter	Healed tuberculosis
19	M	34	American	Clerk	Normal, but examination not completed
20*	M	42	Irish	Laborer	Roentgenographic proof of active tuberculosis
21*	M	56	German	Clerk	Cardiovascular renal condition
22	M	38	German	Machinist	Exophthalmic goiter
23*	M	54	Dutch	Machinist	Healed tuberculosis
24*	M	30	Irish	Waiter	Healed tuberculosis
25*	M	35	Austrian	Laborer	Roentgenographic evidence of active tuberculosis
26*	M	30	American	Electrician	Syphilis
27	M	30	Negro	Laborer	Syphilis, lead poisoning
28*	M	43	American	Electrician	Healed tuberculosis
29*	M	43	German	Cook	Urine contains bile pigment, subject presents a number of other abnormalities
30*	M	42	Irish	Porter	Cardiovascular renal condition
31	F	42	American	Housewife	Exophthalmic goiter
32*	M	26	American	Salesman	Cardiovascular renal condition
33	M	37	American	Laborer	Epileptic
34*	M	41	American	Railroad worker	Changes in capillaries of the skin healed tuberculosis
35*	M	44	German	Clerk	Normal
36*	M	43	American	Clerk	Cardiovascular renal condition
37*	M	45	Irish	Miner	Normal
38	M	39	Jewish	Druggist	Angioneurotic edema
39*	M	35	Polish	Porter	Syphilis
40*	M	40	German	Houseman	Capillaries of the skin abnormal
41*	M	40	English	Machinist	Normal
42*	M	33	American	Fireman	Cardiovascular renal condition (myocarditis)
43*	M	45	American	Steamfitter	Normal
44*	M	48	American	Porter	Normal
45*	M	39	American	Painter	Cardiovascular renal condition
46*	M	29	American	Carpenter	Inanition, died later at Cook County Hospital (bronchopneumonia), fainted during examination
47*	M	38	American	Painter	Healed tuberculosis
48*	M	46	American	Woodworker	Syphilis
49*	M	42	Italian	Laborer	Cardiovascular renal condition
50*	M	20	German	Mason	Normal
51	F	58	German	Housewife	Exophthalmic goiter
52*	M	36	German	Steel worker	Healed tuberculosis
53*	M	39	Swedish	Laborer	Normal
54*	M	49	American	Fireman	Cardiovascular renal condition, probably cirrhosis, myocarditis
55*	M	51	American	Metal worker	Cardiovascular renal condition
56*	M	44	English	Fireman	Roentgenographic evidence of active tuberculosis 3 years before, angioneurotic edema
57	F	39	German	Housewife	Postoperative hypothyroidism, on thyroid extract, with basal metabolic rate +31.5

* One of group of 100 "normal" men

TABLE 1—General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation—Continued

Individual No	Sex	Age	Nationality	Occupation	Clinical Notes
58	F	29	American	Housewife	Exophthalmic goiter
59*	M	37	Irish	Butcher	Normal
60	M	52	American	Salesman	Cardiovascular renal condition
61*	M	51	American	Musician	Cardiovascular renal condition
62*	M	44	American	Carpenter	Cardiovascular renal condition, aortic regurgitation
63*	M	40	American	Fireman	Cardiovascular renal condition
64*	M	31	American	Machinist	Normal, somewhat nervous
65*	M	34	American	Fireman	Cardiovascular renal condition
66*	M	64	American	Engineer	Cardiovascular renal condition
67*	M	47	American	Porter	Dwarf
68*	M	35	American	Draftsman	Healed tuberculosis
69	M	22	Jewish	Student	Duodenal ulcer, nervous, parents both have high blood pressure
70*	M	65	German	Butcher	Cardiovascular renal condition, arthritis deformans
71*	M	42	Scotch	Cook	Cardiovascular renal condition
72*	M	42	Scotch	Laborer	Normal
73*	M	48	American	Engineer	Syphilis
74*	M	49	American	Clerk	Changes in the capillaries of the skin
75*	M	66	American	Laborer	Cardiovascular renal condition
76*	M	43	American	Cook	Cardiovascular renal condition
77*	M	39	Irish	Machinist	Sensitized, drug addict?
78*	M	33	American	Painter	Normal, but with many deviations in examinations
79*	M	58	American	Machinist	Gastric ulcer, occasional peripheral vascular spasms
80*	M	29	American	Electrician	Nervous, has tremor urticaria in 1922
81*	M	69	American	Elevator operator	Cardiovascular renal condition, pruritis
82*	M	66	English	Laborer	Cardiovascular renal condition
83*	M	45	German	Fireman	Normal
84*	M	73	Canadian	Foundry worker	Cardiovascular renal condition
85*	M	45	American	Tile setter	Fever (bronchitis?)
86*	M	50	American	Dentist	Nervous
87*	M	46	American	Chauffeur	Normal
88*	M	55	American	Factory worker	Roentgenographic evidence of active tuberculosis
89*	M	41	Irish	Sailor	Healed tuberculosis
90*	M	30	American	Mail sorter	Nervous
91*	M	91	Irish	Gardener	Cardiovascular renal condition
92*	M	22	Jewish	Student	Nervous
93*	M	53	American	Laborer	Cardiovascular renal condition, hay fever
94*	M	57	American	Laborer	Normal
95*	M	54	German	Cook	Healed tuberculosis
96*	M	70	American	Ironworker	Cardiovascular renal condition
97*	M	53	American	Miner	Normal, nervous
98*	M	34	American	Railroad worker	Cardiovascular renal condition
99*	M	46	Norwegian	Laborer	Healed tuberculosis
100*	M	45	Norwegian	Laborer	Healed tuberculosis
101*	M	55	American	Laborer	Eczema
102*	M	65	American	Metal worker	Roentgenographic evidence of active tuberculosis
103*	M	59	American	Rancher	Cardiovascular renal condition
104*	M	76	American	Laborer	Roentgenographic evidence of active tuberculosis, cardiovascular renal condition
105*	M	56	American	Painter	Healed tuberculosis
106*	M	60	American	Cook	Cardiovascular renal condition
107*	M	62	American	Sailor	Cardiovascular renal condition
108*	M	67	American	Clerk	Roentgenographic evidence of active tuberculosis
109	F	42	American	None	Neurasthenia
110*	M	62	American	Teamster	Healed tuberculosis
111*	M	60	American	Clerk	Cardiovascular renal condition, syphilis 30 years before
112*	M	60	American	Wool sorter	Cardiovascular renal condition
113*	M	59	Irish	Butcher	Cardiovascular renal condition
114*	M	79	English	Engineer	Roentgenographic evidence of active tuberculosis, cardiovascular renal condition
115*	M	66	American	Telegrapher	Cardiovascular renal condition
116	F	30	English	Clerk	Urticaria
117	M	30	English	Stockman	Arthritis, syphilis
118	F	14	American	Schoolgirl	Arthritis, pleural tuberculosis?

* One of group of 100 "normal" men

TABLE 1—General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation—Continued

Individual No	Sex	Age	Nationality	Occupation	Clinical Notes
119	F	43	Dutch	Housewife	Arthritis deformans, adenoma of thyroid with hyperthyroidism
120	F	18	Hungarian	Housework	Purpura
121	F	56	American	Housewife	Arthritis deformans
122*	M	33	American	Instructor	Normal, fatigue, numerous deviations from normal in examinations
123	F	63	American	Housewife	Carcinoma of thyroid, hyperthyroidism, cardiovascular renal condition
124	F	25	American	Nurse	Arthritis with mitral lesion
125	F	29	American	Housewife	Exophthalmic goiter
126	M	21	American	Metal polisher	Exophthalmic goiter
127*	M	65	Irish	Janitor	Cardiovascular renal condition
128*	M	66	American	Railroad worker	Hay-fever, cardiovascular renal condition
129*	M	66	Irish	Janitor	Roentgenographic evidence of active tuberculosis, cardiovascular renal condition
130*	M	65	Irish	Mason	Cardiovascular renal condition
131	F	59	Austrian	Housewife	Exophthalmic goiter
132	M	26	American	Student	Eczema
133	F	29	Jewish	Housewife	Generalized scleroderma
134*	M	67	American	Carpenter	Cardiovascular renal condition
135	M	26	Jewish	Tailor	Nervous
136	M	44	Italian	Laborer	Pellagra, cardiovascular renal condition
137	F	61	Bohemian	Housewife	Glaucoma
138	M	27	Jewish	Salesman	Froehlich's syndrome
139	F	29	American	Stenographer	Vitiligo and urticaria
140	M	45	Irish	Laborer	Glaucoma, cardiovascular renal condition, roentgenographic evidence of active tuberculosis hay fever
141	F	48	Negro	Housewife	Glaucoma, cardiovascular renal condition
142	M	50	American	Machinist	Brain tumor, Cook County Hospital, syphilis 20 years before
143	M	45	Hungarian	Carpenter	Pellagra, cardiovascular renal condition, syphilis
144	M	47	Lithuanian	Carpenter	Pellagra, cardiovascular renal condition
145	M	71	Swedish	Watchman	Glaucoma, syphilis
146	F	40	American	Sewing	Myasthenia gravis
147	F	19	Polish	Operator	Postencephalitic parkinsonism
148	F	67	American	Housewife	Glaucoma, vitiligo, hay fever
149	M	35	American	Salesman	Nervous
150	M	67	Jewish	Teamster	Glaucoma
151	F	68	German	Housewife	Postoperative exophthalmic goiter (no 51)
152	M	27	American	Plumber	Angioneurotic edema
153	M	75	American	Farmer	Glaucoma, cardiovascular renal condition
154	M	55	American	Steel worker	Glaucoma, cardiovascular renal condition
155	M	33	American	Engineer	Postoperative exophthalmic goiter (no 16)
156	F	30	American	Housewife	Postoperative exophthalmic goiter (no 125)
157	M	33	American	Plumber	Postoperative exophthalmic goiter (no 22)
158	M	35	Bohemian	Butcher	Hodgkin's disease
159	M	53	American	Clerk	Exophthalmic goiter
160	M	58	English	Shoemaker	Glaucoma, cardiovascular renal condition, asthma
161	F	43	American	Housewife	Glaucoma, cardiovascular renal condition
162	M	47	German	Railroad worker	Postoperative exophthalmic goiter (no 11)
163	F	29	American	Housewife	Postoperative exophthalmic goiter (no 58)
164	M	48	Cuban	Salesman	Glaucoma, syphilis, cardiovascular renal condition
165	M	52	American	Upholsterer	Glaucoma, cardiovascular renal condition
166	M	24	Hindoo	Student	Asthma, eosinophilia
167	F	77	Swiss	Housewife	Glaucoma, cardiovascular renal condition
168	M	28	American	Physician	Orthostatic albuminuria
169	M	27	American	Chauffeur	Buerger's disease, syphilis
170	F	56	Negro	Servant	Glaucoma, diabetes, cardiovascular renal condition
171	F	23	Jewish	Technician	Urticaria (menstrual)
172	M	30	Greek	Waiter	Raynaud's disease, syphilis in 1921
173	M	39	American	Instructor	Cord tumor
174	F	50	American	Housework	Raynaud's disease







* One of group of 100 "normal" men

Chart 1.—The scale of the blister time (heavy line) of normal persons and patients with various clinical conditions

It will be observed that the blister time varies from a short time of $3\frac{1}{2}$ hours in one case to 15 hours in a group of cases The average for our group of 100 "normal" men is $7\frac{1}{2}$ hours, this is indicated by the horizontal line

Persons of the actually normal group (twenty in number) are designated by a star in the circle, in the first line below the curve The range for these is from 4 to 9 hours As the person (no 122) with the four-hour blister time is abnormal in several other respects, we have not considered 4 hours as within the true normal range The normal range is indicated by the shaded diamond in the center of the chart, in case of normal blister time having been placed between 6 and 9 hours

Individuals of the group who showed healed tuberculosis are indicated by the large crosses in the next line Individuals of the group with cardiovascular renal conditions of the group who gave roentgenologic evidence of healed tuberculosis are indicated by a small cross placed in the same horizontal space The persons with positive Wassermann reactions and those with a clear history of previous syphilis are indicated by W in the same space Patients who gave roentgenologic evidence of active tuberculosis can be identified by a black block in the third horizontal space Those in the various groups of the division with cardiovascular renal conditions can be identified by the devices in the five lowest horizontal compartments, as follows

-  A patient having a low blood pressure (under 110) with the urine containing either albumin or casts
-  A patient having a normal blood pressure (from 110 to 140) with positive evidence of urinary changes
-  A patient having a blood pressure of over 140 with positive evidence of urinary changes
-  A patient having a blood pressure of over 140 with no evidence of changes in the urine
-  A patient having roentgenologic evidence of arteriosclerosis of the larger vessels When this has been found incidental to other clinical conditions, a small circle has been used
-  A person in whom the capillaries of the skin are abnormal A small c has been used to indicate that changes in the capillaries of the skin have been found incidental to other clinical conditions

All the large symbols used in these lower five horizontal columns refer to the group of 100 "normal" men

At the top of the curve we have used G to indicate the patients with glaucoma and \times G to indicate those with exophthalmic goiter In some charts, the individual numbers of the patients have been appended in the uppermost horizontal column

An N along the curve indicates a nervous person, and an S a person who has been sensitized This explanation applies to all charts

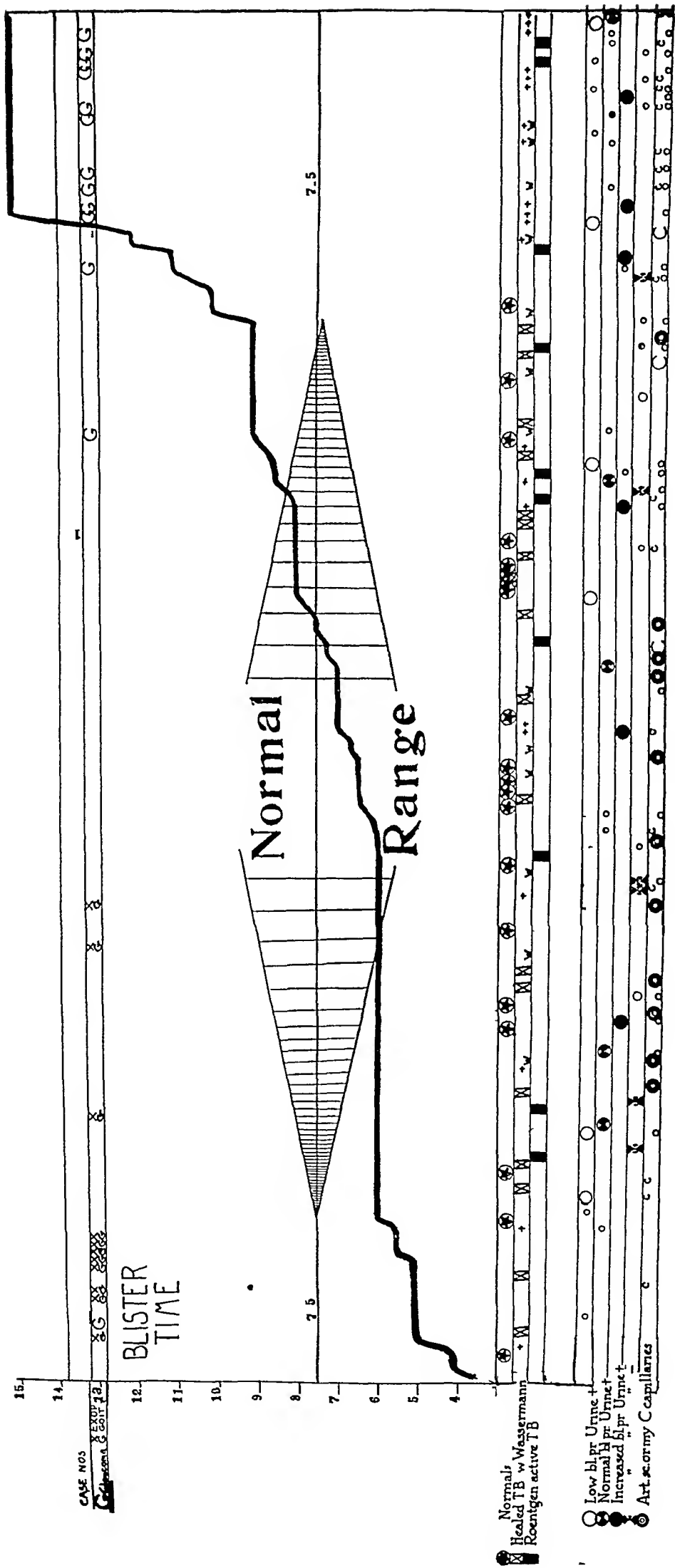


Chart 1

TABLE 2—The Results of Examinations of the Twelve Persons with the Shortest Blister Time

Individual Number	Blister Time, Hours	Diagnosis	Calcium, Mg	Potas- sium, Mg	K/Oa Ratio	Kromayer Light Erythema Time, Minutes	Age	Ice Reaction Time, Seconds	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Atelectasis, Changes in Capillaries Urine
116	3.5	Urticaria	10	19.1	1.91	30	30	20	Vagotonic	20.1	7.4	
69	4	Uter and nervous	9.6	16	1.66	120	22	20	Sympathetotonic	21.2	10	
152	4	Angioneurotic edema	9.8	20.1	2.05	60	27	15	Vagotonic	26	7.5	+
122*	4	Normal	10.6	19.2	1.81		33	5	Vagotonic	20	7.8	
7	4.25	Uter					25					
17*	5	Healed tuberculosis	10.1	26.2	2.51	90	38	15	Vagotonic	21.6	5.2	
121	5	Heart disease, arthritis	10.5			90	25	10	Vagotonic	15.2	2.6	
161	5	Glaucoma	9.17	18.03	1.96	75	13	12	Sympathetotonic	11	13	Trace
171	5	Urticaria	12.66	17.89	1.42	75	23	20	Sympathetotonic	17	10.5	Trace
38	5	Angioneurotic edema	9.8	21	2.11	90	30	10	Vagotonic	18	8.6	
10*	5	Healed tuberculosis	10.1	21.6	2.1	150	40	7	Vagotonic	22.1	8.4	
5	5.5	Neurosis	11.9	25.7	2.16	75	18		Vagotonic			Trace
Averages	4.0		10.4	20.81	2.005	85.5	32.7	13.1		19.58	8.1	

* One of group of 100 "normal" men

† Albumin

TABLE 3—The Results of Examinations of the Twenty-Three Persons with a Prolonged Blister Time of Fifteen Hours

Individual Number	Blister Time, Hours	Diagnosis	Calcium, Mg	Potas sium, Mg	K/Oa Ratio	Kromayer Light Erythema Time, Minutes	Age	Ice Reaction Time, Seconds	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Arterio sclerosis and Changes in Capillaries Urine
167	15	Glaucoma	12	22.7	1.78	120	77	5	Sympathetotonic	17	11	+
150	15	Glaucoma	12	21.3	1.76	95	67	7	Vagotonic	17	14	+
86*	15	Nervous	12.6	15.9	1.26	105	50	25	Vagotonic	18	11	+
115	15	Glaucoma	10.1	15.7	1.55	180	71	20	Sympathetotonic	18	13.6	Arteriosclerosis and Wassermann positive
146	15	Myasthenia gravis	9.2	11.1	1.56	105	40	30	Vagotonic	18	12	+
117	15	Glaucoma	9.7	21.3	2.5	85	67	10	Vagotonic	18	12	+
118	15	Parkinsonism	9.8	19.7	2	105	19	25	Sympathetotonic	18	11.6	+
114	15	Pellagra	9.8	17.6	1.79	120	17	10	Sympathetotonic	11.4	11.5	+
140	15	Pellagra	9.7	16.9	1.74	110	45	15	Sympathetotonic	16.6	11.3	Albumin
158	15	Hodgkin's disease	9.33	18.53	2	60	19	35	Sympathetotonic	19.2	11.3	Albumin
169	15	Buerger's disease	12.34	19.24	1.56	120	27	25	Vagotonic	20.8	11	Wassermann positive
107*	15	Glaucoma	8.1	18.2	2.21	130	61	30	Vagotonic	15.4	10.5	Albumin
154	15	Glaucoma	9.9	23.08	2.36	90	55	20	Sympathetotonic	23.6	10	+
104*	15	Cardiovascular renal condition	10	15.4	1.56	80	67	12	Sympathetotonic	20	9.8	+
106*	15	Pellagra	10	18.8	1.88	105	41	15	Sympathetotonic	20	9.5	+
79*	15	Uter	11.2	20	1.78	210	58	20	Sympathetotonic	19.2	9.1	+
160	15	Glaucoma	10.86	21.58	1.98	70	58	10	Vagotonic	16	8	+
110	15	Glaucoma and tuberculosis	11.1	20.7	2.61	150	15	10	Vagotonic	18	8	+
170	15	Glaucoma	10.6	23.7	2.2		56	56				
129*	15	Tuberculosis	11.5	19	1.65	90	66	17	Vagotonic	18.1	7	Cast
155	15	Glaucoma	9	18.7	2.08	90	75	30	Sympathetotonic	22	6.5	Cast
180	15	Cardiovascular renal condition	10.4	15.5	1.49	120	65	15		20	5.4	Cast
123*	15	Cardiovascular renal condition	10.2	19.7	1.93	210	66	21	Sympathetotonic			Albumin
Averages	15		10.4	19.5	1.83	118	55.1	21.3		18.6	10.1	

* One of group of 100 "normal" men

the curve representing increased blister time, those with exophthalmic goiter are at the end representing shortened blister time

In tables 2 and 3, we present the details of the examinations of the twelve persons with the shortest blister times and of the twenty-three with a blister time of approximately fifteen hours. In practically all other tabulations, we have selected the twenty showing the extreme reactions¹

From tables 2 and 3, the following conclusions seem warranted. Of the twenty-three persons with a prolonged blister time (table 2), twenty show roentgenologic evidence of arteriosclerosis, a positive Wassermann reaction or urinary changes (90 per cent). In the group with the shortest blister times there are none with arteriosclerosis, only one with capillary change and four (25 per cent) with trace of albumin in the urine.

The group in which blister formation is prolonged has a slightly lower level of potassium and a lower K/Ca ratio. The Kromayer light erythema time is longer, as is the reaction to ice. The persons are much older. There are fewer vagotonic reactions to epinephrine and, though the wheal due to the intracutaneous injection of epinephrine hydrochloride is small, the flare is large.

It will be noted that the types of diseases of the one group are different from those of the other group.

CAPILLARY PERMEABILITY

Permeability of the capillaries of the skin, as estimated by the relative proportion of protein in a cantharides blister as compared with the protein in the serum of the capillary blood, averages 62 for the group of 100 "normal" men. In a previous study² of sixty-six normal students in an age group of from 22 to 25, we found the average permeability to be 68, and in another study³ of a small group of young women during the intermenstrual period, we found it to be 72.

The average for our strictly normal group is also 62. When we examine chart 2, we find that a number of the normal persons are grouped at the low end of the scale. In three of the four lowest,

1 Patients with exophthalmic goiter have not been included because we have felt that the extreme changes associated with the disease might tend to distort the averages.

2 Petersen, W. F., and Willis, D. A. Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Skin Blister, *Arch Int Med* **38** 663 (Nov) 1926.

3 Petersen, W. F., and Milles, G. The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, *Arch Int Med* **38** 730 (Dec) 1926.

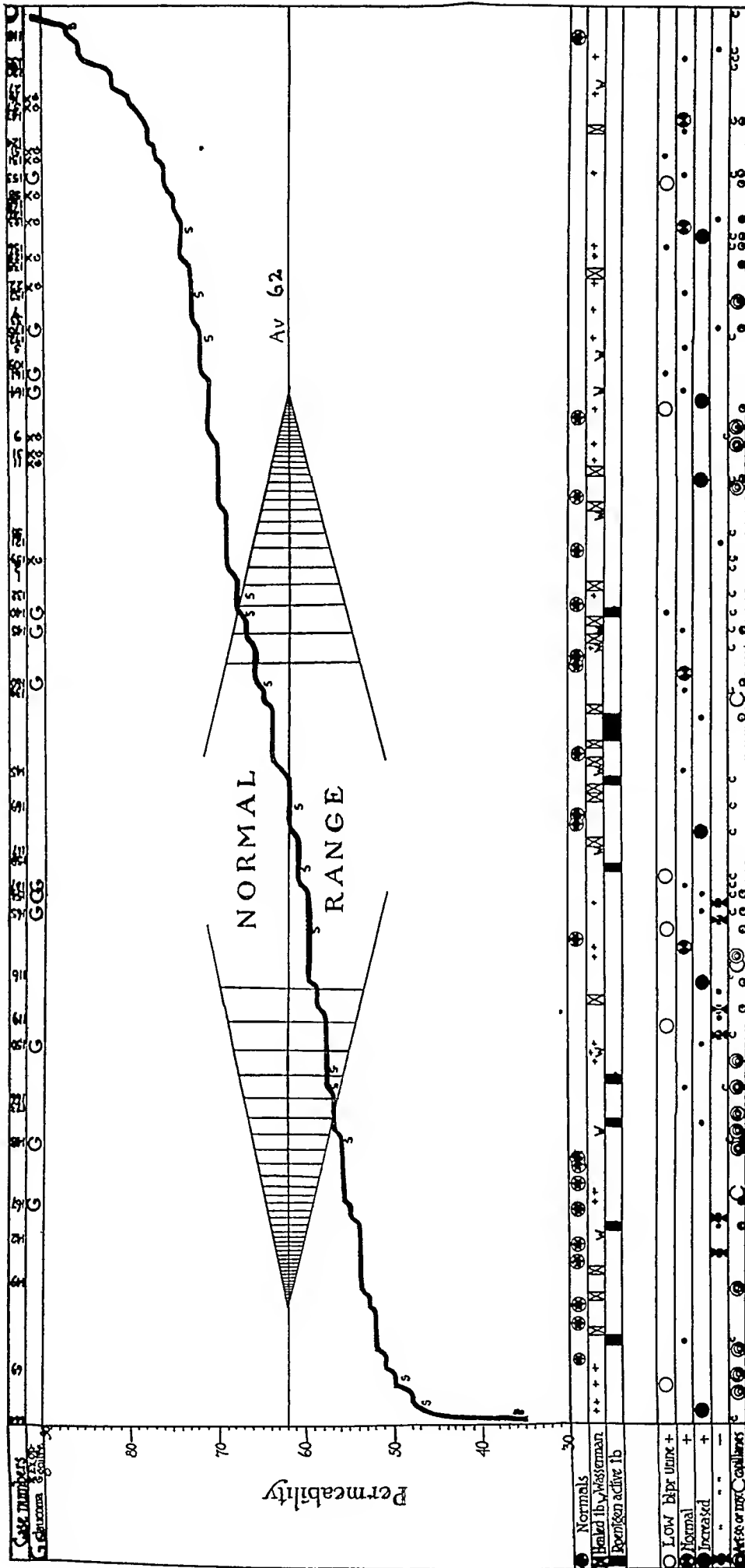


Chart 2—The permeability of the capillaries of the skin (indicated by heavy line) of normal persons and patients with various clinical conditions. An explanation of the grouping of the normal persons and patients along the curve is given in the legend for chart 1.

TABLE 4—*The Results of Examinations of the Twenty Persons Having the Lowest Permeability of the Capillaries*

Individual Number	Permeability of Capillaries	Diagnosis	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Weight/Length Ratio	Age	Changes in Capillaries	Changes in Urine
144	35	Pellagra	14.4	11.5	15	0	174	47	+++	0
115	46	Cardiovascular renal condition	17.2	6.2	14.2	8	215	66		Trace albumin
101	47	Sensitized	19.6	7	10	0	191	53		
42	47	Cardiovascular renal condition	19.2	11.8	9.2	4.6	241	33	Dilatation	
127	50	Cardiovascular renal condition	18.4	9.7	15.4	12	180	65		Albumin, casts
93	50	Cardiovascular renal condition, sensitized	20.4	8.6	10	0	267	52	0	
69	51	Nervous and ulcer	21.2	10	14.4	10.2	160	22	Delayed	
83	51	Normal	17.2	9.2	13.4	11	258	45		
103	52	Cardiovascular renal condition	22.4	9	12.2	0	270	59		
129	52	Tuberculosis, cardiovascular renal condition	18.4	7	12.7	0	249	66	Granulation, sluggish	Casts
89	52	Healed tuberculosis	20.8	9.8	10.2	0	234	41	Slow	
59	52	Normal	22	7.2	15.6	8	252	37		
62	52	Aortic regurgitation	17.2	7	11.4	7.8	221	44		
94	53	Normal	20	6	11.2	7.8	230	57		
100	53	Healed tuberculosis	18.8	8.6	12	29.2	241	45		
112	54	Cardiovascular renal condition	22.4	7.2	9.8	0	218	60		
149	54	Nervous	20	9.7	19	0	209	35	Diminished	
110	54	Edema, healed tuberculosis	20.8	4.2	12	9.4	190	62		
35	54	Normal	22.8	11	9.2	0	203	44		
45	54	Cardiovascular renal condition	20.4	9.8	16.4	12	317	39		
50	Averages and totals		19.6	8.5	12.7	6	224	48.7	2 (granulation)	3

TABLE 5—*The Results of Examinations of the Twenty Persons Having the Highest Permeability of the Capillaries*

Individual Number	Permeability of Capillaries	Diagnosis	Epinephrine, Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Weight/Length Ratio	Age	Changes in Capillaries	Changes in Urine
80	91	Nervous	14.8	12.4	13.4	9.2	212	29	Granulation	
77	87	Sensitized	14	10.8	10	15.4	187	39		
118	87	Arthritis, tuberculosis	16.8	7.4	12	8.6	154	14		
78	86	Normal	19.6	12	12.4	6.2	203	33	Tortuosity Granulation	
79	86	Ulcer	19.2	9.4	8.2	12.2	220	53		
135	84	Nervous	12.4	3.2	20	0	183	26		Casts
120	82	Purpura	21.2	7.2	12.1	0	172	18		
92	82	Nervous	20.4	10.2	15.2	7.6	210	22		
27	82	Lead poisoning and syphilis					217	30		
147	79	Parkinsonism	18	11.6	13	0	142	19	Granulation	
66	78	Cardiovascular renal condition	20	9.2	10.2	6	257	64		+
68	78	Healed tuberculosis	19.2	9.6	12	7	217	35	Rapid flow	Trace albumin
124	78	Arthritis, heart disease	15.2	2.6			210	25	Diminished flow	
153	76	Glaucoma, decompensation	22	6.5	18	0	223	75	Dilatation	+ Casts
76	76	Cardiovascular renal condition	20	6.6	11	7	230	43		Granular casts
168	75	Orthostatic	18	16	14	0	215	28		Albumin
146	75	Myasthenia	18	12	19	0	192	40		
14	74	Cardiovascular renal condition	24.4	6.2	15	5	198	36		Casts
70	74	Cardiovascular renal condition	18	11	10	0	264	65	Slow	Casts, albumin
136	74	Pellagra	20	9.5	18	0	180	44	Granulation	Albumin
80	Averages and totals		18.3	9.1	13.4	4.3	204	37	7 (granulation)	9

the examination of the capillaries of the skin revealed that the capillary flow was sluggish or that the number of capillaries was diminished. While, therefore, we cannot regard these persons as abnormal, the change in the flow of the capillaries of the skin must be considered in connection with their diminished permeability. On the other hand, we note that the end of the scale representing higher permeability reveals more persons in whom distinct anatomic changes could be observed in the capillaries in the form of granulations, marked dilatations, etc.

Healed tuberculosis (revealed by roentgen examination) is found at all levels, but the cases in which there is roentgenologic evidence of active tuberculosis are found at the normal or lower levels of permeability. It should be emphasized that these cases are not necessarily clinically active; in the clinically active cases, the tendency is toward greater permeability with progression of the disease⁴. (In chart 2, persons with roentgenologic evidence of healed tuberculosis other than those of the group of 100 "normal" men are indicated by the cross in the horizontal column designated "Healed Tuberculosis".)

It will be noted that the arteriosclerotic or myocarditic (revealed by roentgen examination) cases are equally common in both regions of the scale. But of the eighteen persons with arteriosclerosis on the side of lower permeability, only five have urinary changes, while of the seventeen on the side of higher permeability, ten have urinary changes.

There are, furthermore, nine with increased blood pressure (over 140), but without urinary changes, in the group of less permeability as compared with four in the group of more permeability.

Capillary changes, i. e., granulations, occur in eleven in the group below the average and in twenty in the group above.

Sensitized persons are reported in all the ranges.

The increased permeability coincident with exophthalmic goiter is apparent.

In table 4, we have tabulated the results of some examinations of the twenty persons with the lowest permeability and in table 5, of those with the highest permeability (excluding those with exophthalmic goiter).

When we examine the averages of tables 4 and 5, we find, of course, that the persons with lessened permeability are older and heavier.

INFLAMMATORY INDEX

The group with low inflammatory indexes is partly identical with a series showing prolonged blister time, i. e., persons of advanced age, with cardiovascular renal lesions or with other evidences of chronic disease.

⁴ Levinson, S. A., and Petersen, W. F. *Am. Rev. Tuberc.* **15**: 681, 1927, part VII, this series.

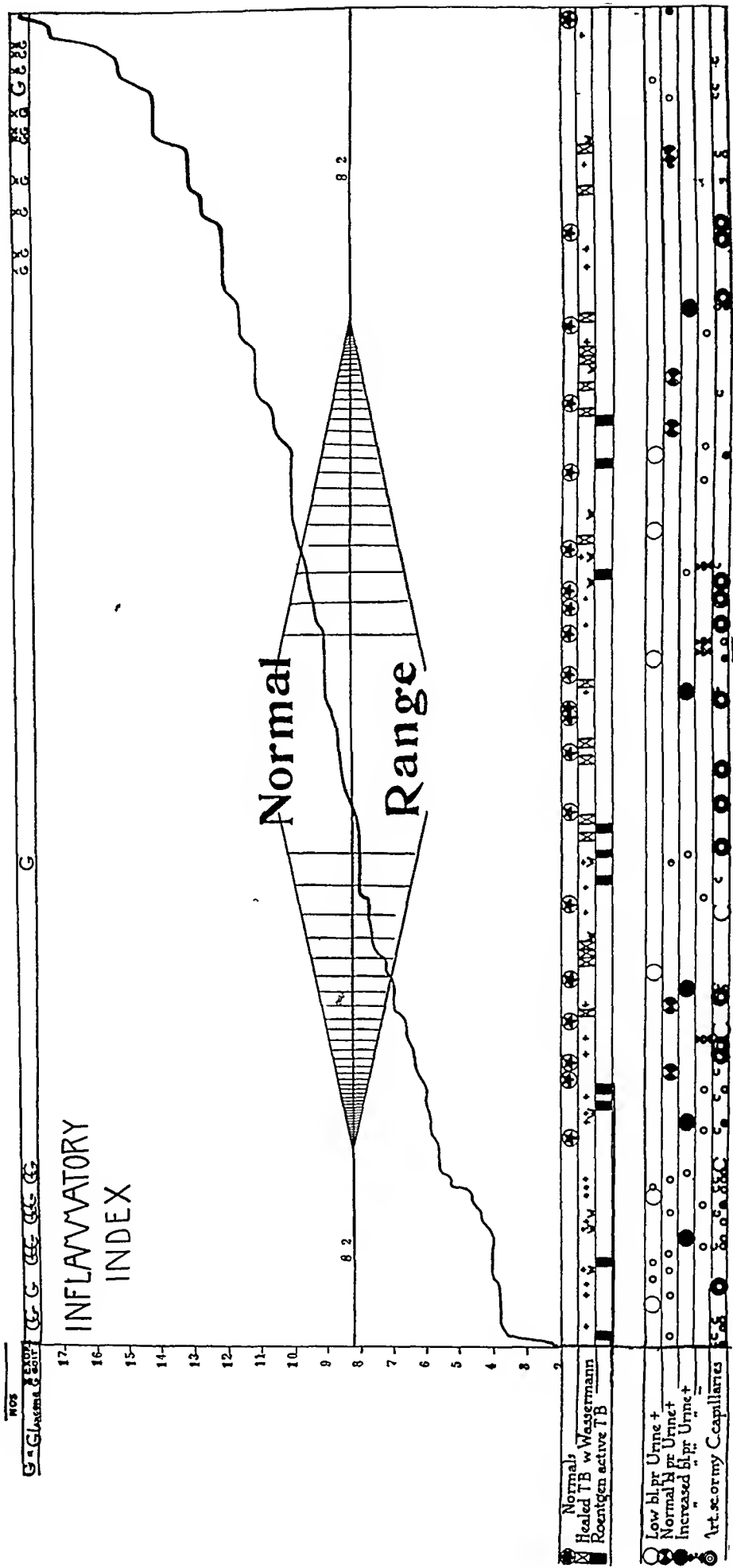


Chart 3—The inflammatory index (heavy line) of normal persons and patients with various clinical conditions

TABLE 6 — The Results of the Examinations of the Twenty Persons Having the Lowest Inflammatory Indices

Individual Number	Inflammatory Index	Diagnosis	Blister Time, Hours	Permeability of Capillaries	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Kromayer Light Erythema Time, Mm	Carbon Dioxide Combining Power	Ice Reaction Time Seconds	Age	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Thyroxin, Wheal (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)
136	5	Pellagra	15	71	10	18.8	1.88	105	57.9	45	44	Sympatheticotonic	20	9.5	18	0
137*	4.7	Cardiovascular renal condition	15	71	10.4	15.5	1.49	120	55.6	45	65	Sympatheticotonic	20	5.4	11.8	0
170	1.6	Aortic syphilis, bronchectasis, glaucoma	15	72	10.5	23.7	2.2		52.5		56					
145	1.1	Glaucoma	15	67	10.1	15.7	1.55	180	55.4	20	71	Sympatheticotonic	18	13.6	16	0
160	1.4	Asthma, emphysema, bronchectasis, glaucoma	15	66	10.8	21.5	1.98	70	62.7	10	58	Vagotonic	16	8	20	0
169	4.1	Buerger's disease	15	62	12.3	10.2	1.56	120	55.1	25	27	Vagotonic	20.8	11	18	0
181*	4	Cardiovascular renal condition	15	60	9.9	15.4	1.56	80	54.8	12	67	Sympatheticotonic	23.6	9.8	19.2	9.6
174	4	Glaucoma	15	60		23		90	56.6	20	66.6	Vagotonic	23	10	26	0
187	1	Cardiovascular renal condition, glaucoma	15	61	8.1	18.2	2.24	130	51.0	30	61	Sympatheticotonic	15.4	10.5	13	0
140	4.05	Cardiovascular renal condition, glaucoma	15	68	11.4	20.7	2.61	150	55.6	40	45	Vagotonic	18	8	27	0
143	1	Pellagra	15	63	9.7	16.9	1.74	100	55.4	15	15	Sympatheticotonic	16.6	11.3	9	0
188	4	Hodgkin's disease, cardiac renal condition	15	61	9.3	18.5	2	60	57.8	35	49	Sympatheticotonic	19.2	11.3	28	0
128*	3.8	Cardiovascular renal condition	15	58	10.2	19.7	1.93	240	58.1	21	66	Sympatheticotonic			11.1	0
150	3.8	Glaucoma	15	58	12	21.3	1.78	95	72.7	7	67	Sympatheticotonic	17	14	16	0
127*	3.8	Cardiovascular renal condition	13	50	12.2	16.2	1.67	255	50.1	16	65	Sympatheticotonic	18.4	9.7	15.4	12
86*	3.8	Nervous	15	58	12.6	15.9	1.26	105	55	25	50	Vagotonic	18.8	11	15.4	12.4
148	3.7	Glaucoma	15	56	9.7	21.3	2.5	85	69.5	10	67	Sympatheticotonic	18	12	17	0
167	3.7	Bronchectasis, glaucoma	15	56	12	22.7	1.9	120	47.9	5	77	Sympatheticotonic	17	14.2	15	0
129*	3.5	Tuberculosis, cardiovascular renal condition	15	52	11.5	19	1.05	90	61.6	17	66	Vagotonic	18.1	7	12.2	0
144	2.2	Cardiovascular renal condition, pellagra	15	35	9.8	17.6	1.76	120	54.4	10	17	Sympatheticotonic	14.1	11.5	15	0
3.97		Averages and totals	14.9	60	10.6	19.64	1.85	121.8	57.48	20	57.4	5 V, 11 S	18.47	10.6	17.14	11.3

* One of group of "normal" men

TABLE 7—The Results of Examinations of the Twenty Persons Having the Highest Inflammatory Indices

Individual Number	Inflammatory Index	Diagnosis	Blister Time, Hours	Permeability of Capillaries	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Kromayer Light Erythema Time, Mm	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds	Age	Vagotonic Sympatheticotonic Vagotonic Sympatheticotonic	Epinephrine, Wheal (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Thyroxin, Wheal (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)
112	18	Angioneurotic edema	4	73	9.8	20.5	2.05	60	63.4	15	27	Vagotonic	26	7.5	9	8
122*	17	Normal	4	63	10.6	19.2	1.81	30	56.8	5	33	Sympatheticotonic	20	7.8	12	9
116	17	Urticaria	3.5	60	10	19.4	1.94	30	57.1	23	30	Vagotonic	20.4	7.4	5	0
80*	15.1	Cardiovascular renal condition, nervous	6	61	8.1	13.7	1.7	100	53.2	30	29	Sympatheticotonic	14.8	12.4	13.4	9.2
124	15	Heart disease	5	78	9.17	18.03	1.96	90	53.7	10	25	Vagotonic	15.2	2.6		
101	14.5	Cardiovascular renal condition, glaucoma	5	72				75	49.4	12	13	Sympatheticotonic	14	13	13	0
38	14	Cardiovascular renal condition, angioneurotic edema	5	69	9.8	21	2.14	90	58.5	10	39	Vagotonic	18	8.6	10.2	10.4
135	14	Neurovascular syndrome	6	84	11.9	19.6	1.65	75	51.5	18	26	Vagotonic	12.4	3.2	20	0
171	14	Urticaria	5	73	12.66	17.89	1.42	75	48.7	20	18		17.5	10.5	18	0
27	13.6	Lead poisoning	6	82	10	21.4	2.14	150	51.9	7	40	Sympatheticotonic	22.4	8.4	9	7.2
10*	13	Neurovascular syndrome, healed tuberculous	5	64	10.1	24.6	2.4		60.4							
66*	13	Cardiovascular renal condition	6	78	11	20	1.82	15	53.1	23	54	Sympatheticotonic	20	9.2	10.2	0
5	13	Nervous	5.5	72	11.9	25.7	2.16	75	63.9		48					
120	13	Purpura	6	82	10	19.9	1.99	75	52.2	14	18		21.2	7.2	12.1	0
47*	12.8	Healed tuberculosis	5	62	10.4	26.2	2.51	90	56.4	15	38	Vagotonic	21.6	5.2	9	0
69	12.7	Ulcer, nervous	4	51	9.6	16	1.66	120	54.8	20	22	Sympatheticotonic	21.2	10	11.4	10.2
79*	12.6		6	76				120	57.6							
98*	12.1	Cardiovascular renal condition	6	73	8.8	17	1.93	105	62.7	15	34	Sympatheticotonic	20	4	11.2	0
78*	12	Normal	7	86	8.4	18.8	2.23	165	62.7	10	33	Sympatheticotonic	19.6	12	12.4	6.2
106*	12	Cardiovascular renal condition	6	71	11.2	19	1.69	90	49.5	30	60	Vagotonic	19.6	7	11.2	0
13.92	Averages and totals		5.3	73.2	10.17	19.9	1.95	93.5	56.07	16.1	34	8 V, 8 S	19	8	11.8	8.6

* One of group of 100 "normal" men

If we examine chart 3, we observe the piling up of persons with arteriosclerosis, capillary changes and evidence of renal disease (albumin or casts) at the low end of the scale. It may also be observed that the majority of the patients with roentgenologic evidence of active tuberculosis are found in the low range, where, too, there are more persons with roentgenologic evidence of healed lesions. The patients with glaucoma and the associated prolonged blister time are also in this region.

The persons with high inflammatory indexes include those with diseases of the skin (urticaria and angioneurotic edema) and, of course, patients with exophthalmic goiter. It may be significant that none of those with increased blood pressure (over 140, with or without renal lesions) are found above the normal maximal range of 11.5.

When we examine tables 6 and 7, with the results of examinations in twenty of the extreme cases, several differences become apparent. The relation to permeability of the capillaries and blister time is, of course, obvious. The group of persons with the low inflammatory indexes are much older, their calcium levels are higher, their K/Ca ratios are lower, their Kromayer light erythema times and their ice reaction times are longer and their flares due to epinephrine and wheals due to thyroxin are larger.

There are proportionately more sympathetotonic persons among those with low than among those with high indexes, despite the fact that persons with cardiovascular renal lesions are found more frequently at the low end of the scale.

CALCIUM, POTASSIUM AND K/CA RATIO

The relation of the calcium and the potassium and the K/Ca ratio of the blood serum of normal persons, as well as of patients ill from various diseases, has been studied with considerable interest in recent years. The relations to the autonomic reactions, in particular, have received much attention. Kylin,⁵ as well as the Kraus school, showed definite relations to asthma⁶ and hyperpnea.⁷

In the previously published results of examinations of "normal" persons, no evidence was presented as to their actual physical normalcy. In our group of 100 "normal" men, only twenty could actually be as classified. The remaining eighty showed evidence of cardiovascular renal abnormality, healed or active tuberculosis, syphilis, etc.

5 Kylin, E. Acta med Scandinav (suppl) **1** 112, 1927

6 Kylin, E. Klin Wchnschr **6** 1742, 1927

7 Kylin, E. Zentralbl f inn Med **48** 431, 1927

Our determinations were made on fresh serum with the Clark-Collip method for calcium and the Kerr modification for potassium. The results have been tabulated in table 8.

Chart 4 may aid in making the conditions more apparent. It will be noticed that the K/Ca curve commences with a low ratio of 1.12 in a young man (no. 132) 25 years of age (whose interesting series of clinical manifestations of disease we have described on page 220) and reaches a high ratio of 3.22 in a man 52 years of age (no. 93), who has had hay-fever each fall, is sensitive to halibut, shows x-ray evidence of myocarditis and is short of breath on exertion.

When we analyze the K/Ca ratios of the so-called normal group of 100, several interesting relations are to be observed.

Normal Persons—In the first place, the actually normal persons fall, with two exceptions, within the range from 1.7 to 2.4. One of the two exceptions, with a ratio of 1.53, gives a markedly vagotonic reaction to epinephrine. The other, with a ratio of 2.9, is apparently healthy in every respect.

Persons with Roentgenologic Evidence of Healed Parenchymal Tuberculosis and Syphilis—Of the seventeen persons with roentgenologic evidence of healed parenchymal tuberculosis, who are otherwise normal, eleven fall within the normal range, while seven of the nine syphilitic persons are also included within these limits. Tuberculosis, unless active, and syphilitic infection apparently do not materially alter the status.

Persons with Active Tuberculosis—When one now turns to the group with roentgenologic evidence of active tuberculosis, one meets an interesting change. The average ratio for the entire group is 2.08, i. e., normal, but inspection of the chart will reveal that the ratios in the active cases are all outside the normal limits. Five persons have low ratios. Of these, one has albuminuria. These five all have low or normal blood pressure. The other five are at the extreme opposite end, with high K/ca ratios. Three of these have increased blood pressure, one normal blood pressure with albuminuria and the fifth a history of angioneurotic edema.

Persons with Cardiovascular Renal Lesions—The persons with cardiovascular renal lesions are found scattered over the entire range of the K/Ca ratio without any apparent relation to blood pressure, to the degree of sclerosis of the larger vessels (made apparent on roentgen examination) or to capillary changes. There are no true cases of primary hypertension in the group, there being only some with an increase in blood pressure of from 140 to 170 (without changes in the kidneys),

TABLE 8—*The K/Ca Ratios, the Potassium Values and the Calcium Values of One Hundred So-Called Normal Persons, as Well as of Patients with Glaucoma, Exophthalmic Goiter, Etc*

Individual Number	K/Ca Ratio	Calcium, Mg	Potassium, Mg
132	1.12	13.4	15
46*	1.24	13.8	17.4
86*	1.26	12.6	15.9
62*	1.3	12.2	15.2
133	1.32	13.2	17.5
90*	1.34	11.4	14.5
110*			
Edema under eyes, roentgenographic evidence of healed tuberculosis	1.34	12.1	16.3
118	1.4	12.2	17.2
88*	1.4	9.4	13
112*	1.4	12.6	18
171	1.4	12.66	17.9
173	1.43	12.7	18.7
17†	1.43	12.7	18.2
77*	1.44	10.8	15.6
70*	1.45	11.4	16.6
18*	1.46	14.5	21.2
108*			
Roentgenographic evidence of active tuberculosis, chronic	1.47	10.4	15.3
3*	1.47	11.1	16.7
45*			
Increased blood pressure† (had nephritis as a result of scarlet fever)	1.48	11.2	16.6
130*	1.49	10.4	15.5
109	1.5	10.8	16.1
82*	1.5	11.4	17.2
22	1.5	12.1	18.2
20*	1.53	11.4	17.4
134*	1.56	9.9	15.6
60	1.56	11.4	17.5
15*	1.55	12.1	18.8
111*	1.55	11.8	18.3
145	1.55	10.1	15.7
42*	1.56	11.4	17.8
146	1.56	9.2	14.4
169			
Sensitized, healed tuberculosis, Buerger's disease, syphilis	1.56	12.34	19.24
102*	1.63	10.6	17.3
172	1.64	13	21.3
129*			
Roentgenographic evidence of active tuberculosis, nephritis	1.65	11.5	19
135	1.65	11.9	19.6
69			
Nervous, increased blood pressure, ulcer, healed tuberculosis	1.66	9.6	16
65*	1.67	9.8	16.4
106*	1.69	11.2	19
127*	1.68	9.7	16.2
131	1.7	10.6	18
80*			
Nervous, changes in capillaries, healed tuberculosis, previously sensitized	1.7	8	13.7
40*	1.73	10.8	18.7
72†	1.73	10.8	18.7
73*	1.74	11.2	19.5
143	1.74	9.7	16.9
149	1.74	10.1	17.4
14*	1.75	11.2	19.6
44†	1.76	10	17.6
75*	1.78	10.8	19.2
79*	1.78	11.2	20
84*	1.78	10	17.8
150	1.78	12	21.3
165	1.79	10	17.95
144	1.79	9.8	17.6
117	1.8	9.2	17.5
85*	1.8	10.6	19.1
74*	1.8	11	19.9
6	1.8	10.5	18.9
4†	1.8	11.8	21.2
89*	1.81	9.2	16.7
105*	1.81	9	17.1
122†	1.81	10.6	19.2
66*	1.82	11	20
113*	1.82	10.2	18.6
63*	1.83	11.4	20.9
126	1.83	9.8	18.3
64†	1.84	9	16.6
99*	1.86	9.6	17.9
76*	1.87	10.8	20.2
103*	1.88	9.2	17.3
136	1.88	10	18.8
138	1.88	10.6	19.9
Frohlich syndrome (?), myocarditis (?)			

* Indicates that the person is one of the group of 100 so called normal persons

† Indicates that the person is apparently normal on examination

‡ Changes in capillaries means increased dilatation or actual granulation and tortuosity

§ Blood pressures of 140 or over are noted as increased

TABLE 8—*The K/Ca Ratios, the Potassium Values and the Calcium Values of One Hundred So-Called Normal Persons, as Well as of Patients with Glaucoma, Exophthalmic Goiter, Etc—Continued*

Individual Number		K/Ca Ratio	Calcium, Mg	Potassium, Mg
168	Orthostatic albuminuria	1.88	9.4	17.7
43*†	Normal	1.89	9.2	19.4
164	Nephritis, glaucoma, syphilitic aortitis	1.89	8.7	16.54
139	Urticaria, vitiligo, changes in capillaries	1.9	9.7	18.4
167	Glaucoma, arteriosclerosis, changes in capillaries	1.9	12	22.72
16	Exophthalmic goiter, healed tuberculosis, changes in urine	1.9	11.4	21.6
39*	Syphilis	1.91	9.1	18
98*	Arteriosclerosis	1.93	8.8	17
128*	Arteriosclerosis, healed tuberculosis, albumin, changes in capillaries	1.93	10.2	19.7
68*	Healed tuberculosis	1.94	8.8	17.1
116	Urticaria	1.94	10	19.4
59*†	Normal	1.95	9.6	18.8
115*	Arteriosclerosis, albumin	1.95	7.8	15.2
142	Neoplasm (syphilis), arteriosclerosis	1.95	9.4	18.3
180	Neoplasm (mole)	1.96	11.11	21.86
161	Glaucoma, albumin, changes in capillaries	1.96	9.7	18.03
160	Glaucoma, healed tuberculosis, asthma	1.98	10.86	21.6
120	Purpura, changes in capillaries	1.99	10	19.9
174	Raynaud's disease?	2	10.8	21.5
158	Hodgkin's disease	2	9.33	18.53
147	Epidemic encephalitis	2	9.8	19.7
71*	Arteriosclerosis	2	8.8	17.5
67*	Dwarf	2	8.8	17.6
52*	Healed tuberculosis	2	10.4	20.9
8*†	Normal	2	10.5	21
1	Nervous	2	12.1	24.9
2	Epilepsy, angioneurosis	2	12.9	26.1
9	Exophthalmic goiter, changes in capillaries	2.04	11.5	23.5
152	Angioneurotic edema, hyaline casts	2.05	9.8	20.1
101*	Healed tuberculosis, eczema	2.06	9.4	19.4
96*	Arteriosclerosis	2.07	8.2	17
94*†	Normal	2.08	8.4	17.5
153	Glaucoma, nephritis, healed tuberculosis	2.08	9	18.7
119	Adenoma of thyroid	2.1	9	18.7
24*	Healed tuberculosis	2.12	11.7	24.8
27	Syphilis, lead poisoning	2.14	10	21.4
38	Angioneurotic edema, changes in capillaries	2.14	9.8	21
58	Exophthalmic goiter	2.15	12	25.9
5	Healed tuberculosis	2.16	11.9	25.7
41*†	Normal	2.16	9.8	21.2
36*	Albuminuria	2.17	12.1	26.3
123	Carcinoma of thyroid, arteriosclerosis	2.17	9.2	20
159	Exophthalmic goiter	2.17	8.23	17.9
23*	Healed tuberculosis	2.19	13.1	28.6
28*	Healed tuberculosis	2.17	11	24.1
170	Diabetes, etc, glaucoma, increased blood pressure	2.2	10.6	23.71
11	Exophthalmic goiter, healed tuberculosis	2.21	10.9	24.1
78*†	Normal	2.23	8.4	18.8
137	Glaucoma, albuminuria	2.24	8.1	18.2
37*†	Normal	2.26	10	22.6
121	Increased blood pressure, arthritis deformans	2.27	8.9	20.2
166	Eosinophilia of unknown origin	2.27	9.1	20.66
49*	Hyaline casts	2.29	11	25.2
107*	Arteriosclerosis, myocarditis	2.3	8	18.4
83*†	Normal	2.3	8.2	19
87*†	Normal	2.32	8.4	19.5
92*	Neurosis	2.32	8.4	19.5
30*	Arteriosclerosis, increased blood pressure	2.33	10.3	24
61*	Arteriosclerosis, changes in capillaries, albuminuria	2.35	7.6	17.6
97*†	Normal (nervous)	2.37	8.4	20.9
100*	Healed tuberculosis	2.38	9	21.5
29*†	Normal	2.39	10	23.9
114*	Tuberculosis, arteriosclerosis, nephritis	2.4	8	19.2
50*†	Normal	2.4	11.4	27.4
10*	Healed tuberculosis	2.4	10.1	24.6
95*	Healed tuberculosis	2.41	7.8	18.8
13*	Healed tuberculosis	2.48	9.6	23.8
148	Glaucoma, vitiligo, arteriosclerosis	2.5	9.7	24.3
47*	Healed tuberculosis	2.51	10.4	26.2
21*	Albuminuria, changes in capillaries	2.51	10.2	25.6
56*	Tuberculosis, has had angioneurotic edema	2.52	9.8	23.6
51	Exophthalmic goiter	2.58	10	25.8
25*	Tuberculosis, albuminuria	2.6	11.1	28.8
140	Glaucoma, tuberculosis, sensitized	2.61	11.4	29.7
26*	Syphilis	2.61	10.2	26.6
33	Epileptic	2.73	9.5	26.1
32*	Increased blood pressure	2.73	9.5	26.1
48*	Syphilis	2.87	9.6	27.6
34*	Changes in capillaries	2.89	9.6	27.7
35*†	Normal	2.9	8.7	25.2
81*	Arteriosclerosis, myocarditis, pruritis	3.07	8.4	25.8
104*	High blood pressure, tuberculosis, arteriosclerosis	3.09	7.4	22.9
55*	Albumin and hyaline casts, healed tuberculosis	3.1	8	24.9
93*	Sensitized, myocarditis	3.2	7.6	24.5

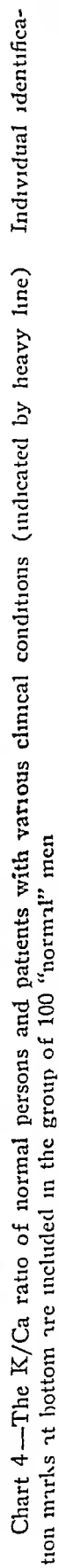


Chart 4.—The K/Ca ratio of normal persons and patients with various clinical conditions (indicated by heavy line). Individual identification marks at bottom are included in the group of 100 "normal" men.

but these are all in persons of advanced age. With one exception, the members of this group all have sthenic hearts.

"Nervous" Persons—The so-called nervous group seems, without doubt, to be associated with changes in the K/Ca ratios. One must, however, consider the possibility that the changes in the ratios are secondary to the nervous conditions rather than the cause of these. Perhaps some of the symptoms (feeling of weakness, etc.) may be sought in an alteration of the salt balance. These cases include the following:

CASE 86—A former dentist, American, 50 years of age, had always been the most nervous one of his family. A sister had exophthalmic goiter. The patient had an attack of angioneurotic edema when a dental student. He used alcohol excessively. The death of a child precipitated a "breakdown." He lost his practice and his family, and became "down and out." He worked occasionally as a janitor.

It may be noticed that the sugar and the globulin were increased, the total protein was low, the muscle reactivity was increased and the reaction to epinephrine hydrochloride was vagotonic. The weight/length ratio was diminished.

CASE 90—A mail sorter, 30 years of age, complained that since the year previously he got "rattled" easily and was nervous. He was extremely sensitive to venipuncture. The family history was negative. The patient reacted markedly to epinephrine with a tremor and a feeling of discomfort. The weight/length ratio was diminished. The intracutaneous reactions to morphine and epinephrine (the flare) were increased, those to thyroxin were diminished. The capillaries of the skin were reduced in number.

CASE 173—A highly successful and intelligent American business man, 40 years of age, with cord tumor, had suffered from incidental worry for two years. The family history was negative other than that the mother was nervous and died from tuberculosis.

The K/Ca ratio in December, 1927, was 1.57 (calcium, 13.5, potassium, 21.3). The K/Ca ratio in May, 1928, was 1.43 (calcium, 12.7, potassium, 18.17). The sugar was 80, the globulins were diminished, the skin resistance was low, the blood pressure was low and the pulse rate was high. The patient reacted strongly to epinephrine. The weight/length ratio was diminished. The intracutaneous reactions to epinephrine were increased, flares due to morphine, thyroxin and caffeine were absent.

CASE 3—A highly intelligent Jewish chemist, 25 years of age, had been nervous for several years. The father suffered from Raynaud's disease.

The patient's reaction to epinephrine was vagotonic. The weight/length ratio was normal. The intracutaneous reactions to thyroxin and caffeine (wheals and flares) were diminished.

CASE 109—An American spinster, 42 years of age, spent much of her time in bed because of "weakness." She had a unilateral ovariectomy fifteen years previously. She menstruated normally. She complained of palpation, nervousness, weakness and excessive perspiration. One sister had an exophthalmic goiter. The mother, 72 years of age, was nervous, with a blood pressure of 160.

The reaction to epinephrine was slightly sympathetictonic, the weight/length ratio low (140), the skin reactions to ice and the Kromayer light faint and the intracutaneous reactions to thyroxin (flares) increased.

CASE 135—A Jewish tailor, 26 years of age, was nervous. The mother died of "shock" following an air raid during the war. The patient had lost 15 pounds (6.8 Kg) during the last year. The reaction to epinephrine was vagotonic. The weight/length ratio was low. The urine showed granular casts. The capillaries of the skin showed granulations. A healed parenchymal tuberculosis was revealed by the x-rays. The globulins were increased. The pharmacologic skin reactions to epinephrine and morphine (wheals and flares) were reduced, the wheals due to thyroxin and caffeine were increased, and the flares were absent.

CASE 69—A Jewish medical student, 22 years of age, alert and intelligent, had a duodenal ulcer and was nervous. He had an occasional tremor. His blood pressure was increased. The mother was nervous and had high blood pressure (210), the father was nervous and had high blood pressure (175). The patient felt weak when blood was drawn. He gave a marked reaction to epinephrine, he felt ill, had a headache and turned pale, and the vascular reaction was markedly sympathetictonic. The weight/length ratio was low. The pharmacologic skin reactions to epinephrine and thyroxin (wheals and flares) were increased, the wheal due to caffeine was increased.

CASE 80—An American electrician, 30 years of age, was nervous and had a tremor. He became nervous in 1924 after an explosion in a salt mine. He had urticaria in 1922.

The reaction to epinephrine was not marked. The reaction to the Kromayer light was marked and the capillary permeability was high. The resistance of the skin to electric current was high. The weight/length ratio was normal. All flares due to the pharmacologic substances employed in the intracutaneous injections were increased. The wheal due to epinephrine was diminished and that from thyroxin was increased. The capillaries of the skin showed beginning granulations.

CASE 149—An American plumber, 35 years of age, had had financial reverses, and was nervous and sleepless. The family history was negative, except for tuberculosis.

The reaction to epinephrine was not marked. The Kromayer light erythema time was shortened, the skin resistance was high and the weight/length ratio was relatively low. The serum globulins were practically absent. The pharmacologic skin reactions to epinephrine were negative, the flares due to other intracutaneous injected substances were reduced or absent and the wheal due to thyroxin was increased.

CASE 1—A Jewish medical student, 23 years of age, who had a "nervous breakdown" a year before examination, felt weak and had a tremor.

The reaction to epinephrine was marked, the sugar was increased and the Kromayer light, ice and blister reactions were delayed. The weight/length ratio was low. The intracutaneous injection of epinephrine hydrochloride and morphine left the skin unchanged, the wheal and the flare due to thyroxin were increased.

CASE 92—A Jewish medical student, 23 years of age, was nervous and unable to concentrate, and had a feeling of weakness and an occasional tremor. He had bowel movements once or twice a week, he sweat easily. The father died from hypernephroma, the mother had periarteritis nodosa (?). The reaction to epinephrine was marked. The blister time and ice reaction were delayed. The

reaction to the Kromayer light was faint. The skin resistance was increased. The weight/length ratio was normal. The intracutaneous reactions to epinephrine and morphine were normal. Those to thyroxin were increased.

The K/Ca Ratio—In a previous examination of this material in its relation to the vascular reaction to epinephrine⁸ it was found that a small group of outstandingly sympathetotonic persons had low K/Ca ratios as compared with the vagotonic ones. We mentioned, however, that many exceptions were observed.

It is apparent that certain disturbances closely associated with a vascular supply are definitely associated with an alteration of the K/Ca ratio. These manifestations take the form of lesions of the skin, lesions of the gastro-intestinal tract, respiratory diseases (hay-fever, asthma, etc.), glaucoma, etc. A change of the K/Ca ratio may influence the permeability of the endothelial cells, which would result in instability and a probable tendency to sudden alterations producing not only edema but other local disturbances of cell function with pruritis, sclerosis, atrophy, etc. Such a change may also involve the contractile mechanism of the vessels including both capillary and arteriole and arterial elements, through the autonomic nervous supply.

It seems probable that the higher centers may play a rôle in this vegetative reorientation. Our results make it evident that the majority of the so-called nervous persons have a low ratio. In this change, the calcium is less involved than the potassium, the calcium may range from high to normal, but the potassium is usually found to be low.

We have the impression that this may result from mental disturbances. It is difficult, however, to determine whether mental disturbances precede the change in the chemical blood picture or follow as a result of it. Tómasson,⁹ in a series of carefully conducted examinations of persons with psychic disturbances, found that the K/Ca ratio showed alterations before the onset of the mental upset. Certainly, a mere examination of the calcium is insufficient to supply us with the necessary information. In view of the close connection between the mental state and the functioning of certain of the endocrine glands, the change in the K/Ca ratio with change in the mental condition should not surprise us.

It seems probable that it is the abnormality of the ratio rather than its change in any one direction that brings about functional vascular disturbances and with this certain manifestations of disease. Thus, one

⁸ Petersen, W. F., Levinson, S. A., and Arquim, S. The Relation of the Reaction to Epinephrine to the Potassium-Calcium Ratio and Other Ratios, *Arch. Int. Med.* **42**: 256 (Aug.) 1928.

⁹ Tómasson, H. *Blodets Elektrolyter, etc.*, Copenhagen, Levin & Mungsgaard, 1927.

may examine the history of two persons who are, respectively, at the bottom and the top of the K/Ca scale

CASE 132—A medical student, 26 years of age, alert and intelligent, had a K/Ca ratio of 1.12. He was the son of a physician. When 12 years of age, he had severe attacks of hyperacidity and dizziness with vomiting. These attacks would occur intermittently several times a month and usually lasted a day, they were relieved by food. The attacks became milder until 1918, then they became more severe. He was free from them at the time of examination. In 1919, he had a severe attack of hiccup, which lasted for forty-eight hours. From 1918 to 1921, he was bedridden with tuberculosis of the right lung. During the course of the tuberculosis, he suffered severely from night sweats. He had hay-fever from the time that he was a young boy until 1919, when it disappeared, and at various times in 1918 he suffered from urticaria. In 1920, he had influenza, associated with a mastoiditis. Since 1919, he had had ulcerative colitis with the possibility of a duodenal ulcer. For one week in 1919, he had diabetes insipidus. During the past three years, he had had hypo-acidity. At the time of examination he was apparently well, except for chronic eczema in both hands. Physical examination revealed no marked changes.

The x-ray picture of the chest was practically negative. However, he had an eosinophilia of from 10 per cent to 14 per cent, and stated that he had never been able to alkalinize the urine, despite large doses of bicarbonate.

CASE 93—An American laborer of Irish extraction, 53 years of age, rather alert, intelligent and somewhat irritable, had a K/Ca ratio of 3.2. He had always done heavy work. He was a periodic drinker until four years before. He had had hay-fever and asthma all of his life. He was attacked by these in the fall, and he stated that he was sensitive to ragweed. For the past fifteen years, he had been sensitive to halibut. X-ray examination revealed evidence of a myocarditis, and he complained of shortness of breath. The family history was apparently negative.

Calcium—The lowest amount of serum calcium, 7.4 mg per hundred cubic centimeters, occurs in a patient (no. 104) with roentgenologic evidence of active tuberculosis and a coincident high blood pressure, the largest amount, 14 mg per hundred cubic centimeters, occurs in a patient with healed parenchymal tuberculosis. The actually normal group have a range of calcium values from 8.2 to 12.7 mg.

In Table 9, some of the observations on the twenty persons having the highest levels of calcium (averaging 12.7 mg per hundred cubic centimeters) have been tabulated. The corresponding observations on the persons with outstandingly low levels of calcium are tabulated in table 10. In order to facilitate comparison, table 11 brings together the averages for the group with high levels of calcium, the group of 100 "normal" men and the group with low levels of calcium.

In chart 5, the normal ranges of the calcium levels are presented. The persons with healed tuberculosis are more frequently in the normal range or the high range, while those with roentgenologic evidence of active tuberculosis are scattered. There appears to be no correlation of these conditions with the cardiovascular condition.

TABLE 9—*The Results of Examinations of the Twenty Persons with the Highest Levels of Serum Calcium*

Individual Number	Diagnosis	Carbon Dioxide Combining Power	Sugar, Mg	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheel (Diameter, Mm)	Thyroxin, Wheel (Diameter, Mm)	Blood Pressure Systolic Diastolic	Pulse Rate	Permeability of Capillaries
18	Healed tuberculosis	58.4	70.2	2	1	10	Vagotonic			129	89	70
46	Inanition.	55.2	61	2	1.70	15	Sympatheticotonic	21.2	12.2	140	82	59
122	Eczema	49.3	67		0.31	10	Vagotonic	18.4	12.6	132	78	68
123	Scleroderma	50.2	77		0.70	29	Sympatheticotonic			92	63	56
23	Healed tuberculosis	57.4	85	3	0.42	23	Vagotonic	17.2	7.2	105	53	67
172	Raynaud's disease		76		0.93	45	Sympatheticotonic	22.4	18	103	78	72
2	Epilepsy	55.6	74		0.10		Sympatheticotonic			100	63	69
173	Worry	55.7	89		0.69	15	Sympatheticotonic	21	13	106	63	57
17	Normal	59.1	61.5	6	0.22	20	Vagotonic	20.8	20.6	130	70	66
86	Nervous	55	94	1.4	0.26	25	Vagotonic	18.8	15.4	118	60	53
171	Urticaria	48.7	72		0.65	20	Sympatheticotonic	17.5	18	114	66	73
112	Arteriosclerosis	57	63	2.4	2.70	18	Vagotonic	22.4	9.8	129	86	54
169	Buerger's disease	55.1	67		0.23	25	Sympatheticotonic	20.8	18	118	78	62
62	Aortic regurgitation	56.8	67	5	0.15	15	Vagotonic	17.2	11.4	140	40	52
115	Chronic arthritis, pterygoid	54.2	89	2.8	1.99	12	Vagotonic	16.8	12	120	69	87
127	Nephritis	59.1	81	2	1.20	16	Sympatheticotonic	18.4	15.4	106	76	59
110	Healed tuberculosis	57.2	61	2	0.69	39	Vagotonic	20.8	12	110	62	54
22	Exophthalmic goiter	52	91	3	0.17	5	Sympatheticotonic	25.4	5	144	74	73
15	Healed tuberculosis	57.6	70	6	0.19	38	Sympatheticotonic	23.2	11.6	123	63	63
1	Nervous	62.1	113		0.11	25	Sympatheticotonic	20	13.2	152	74	63
Averages and totals		56.2	75.7	2.2	0.61	21	9 V, 11 S	20.2	12.6	120	69	64

TABLE 10—*The Results of Examinations of the Twenty Persons with the Lowest Levels of Serum Calcium*

Individual Number	Diagnosis	Carbon Dioxide Combining Power	Sugar, Mg	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheel (Diameter, Mm)	Thyroxin, Wheel (Diameter, Mm)	Blood Pressure Systolic Diastolic	Pulse Rate	Permeability of Capillaries
104	Tuberculosis, arteriosclerosis	57.2	55	1.2	0.63	25	Vagotonic	20.8	12	176	100	54
93	Myocarditis, hay fever	57	70	2.4	0.25	12	Vagotonic	20.4	10	113	71	50
61	Arteriosclerosis	53.1	72	7.4	0.28	7	Vagotonic	19.6	12.4	142	82	70
95	Healed tuberculosis	61.6	77	1.6	0.39	10	Sympatheticotonic	23.6	12	110	63	59
115	Arteriosclerosis	51.8	69	2	0.23	10	Vagotonic	17.2	14.2	148	84	46
55	Nephritis	53.6	73	0.6	0.33	20	Vagotonic	17.6	11.2	123	63	69
89	Nervous	53.2	69	3.8	1.6	39	Vagotonic	14.8	12.4	116	63	91
114	Tuberculosis	69.6	75	4	0.14	25	Sympatheticotonic	20.4	12	174	69	64
107	Myocarditis, arteriosclerosis	55.2	60	2.8	0.23	15	Vagotonic	20.8	13.4	134	72	53
127	Glaucoma	51.9	73	0.8	1.99	30	Vagotonic	15.4	13	119	67	61
83	Normal	53.1	63	4	0.16	20	Vagotonic	17.2	12.4	114	64	51
95	Arteriosclerosis	53.4	77	1.6	0.11	49	Vagotonic	18	12.4	149	85	57
159	Exophthalmic goiter	54.8	71		0.22	7	Sympatheticotonic	25	12	122	63	69
81	Myocarditis, arteriosclerosis	57	63	2.3	0.19	45	Vagotonic	14	10	144	63	59
97	Normal	57.2	60	4.5	0.22	29	Sympatheticotonic	19.2	12	109	62	54
92	Nervous	56.8	67	2.9	0.57	20	Sympatheticotonic	20.4	15.2	110	69	82
87	Normal	55.4	94	3.5	0.42	13	Sympatheticotonic	16	12	104	62	56
78	Normal	62.7	67	1	0.62	10	Sympatheticotonic	19.6	12.4	122	70	86
25	Normal	57.6	79	1.8	0.28	29	Vagotonic	22.8	9.2	168	78	54
164	Syphilis glaucoma	55.6	65		0.23	15	Vagotonic	18		110	75	71
Averages and totals		56.1	69.7	2.6	0.43	19.3	12 V, 7 S	19	12.3	127	71	62.6

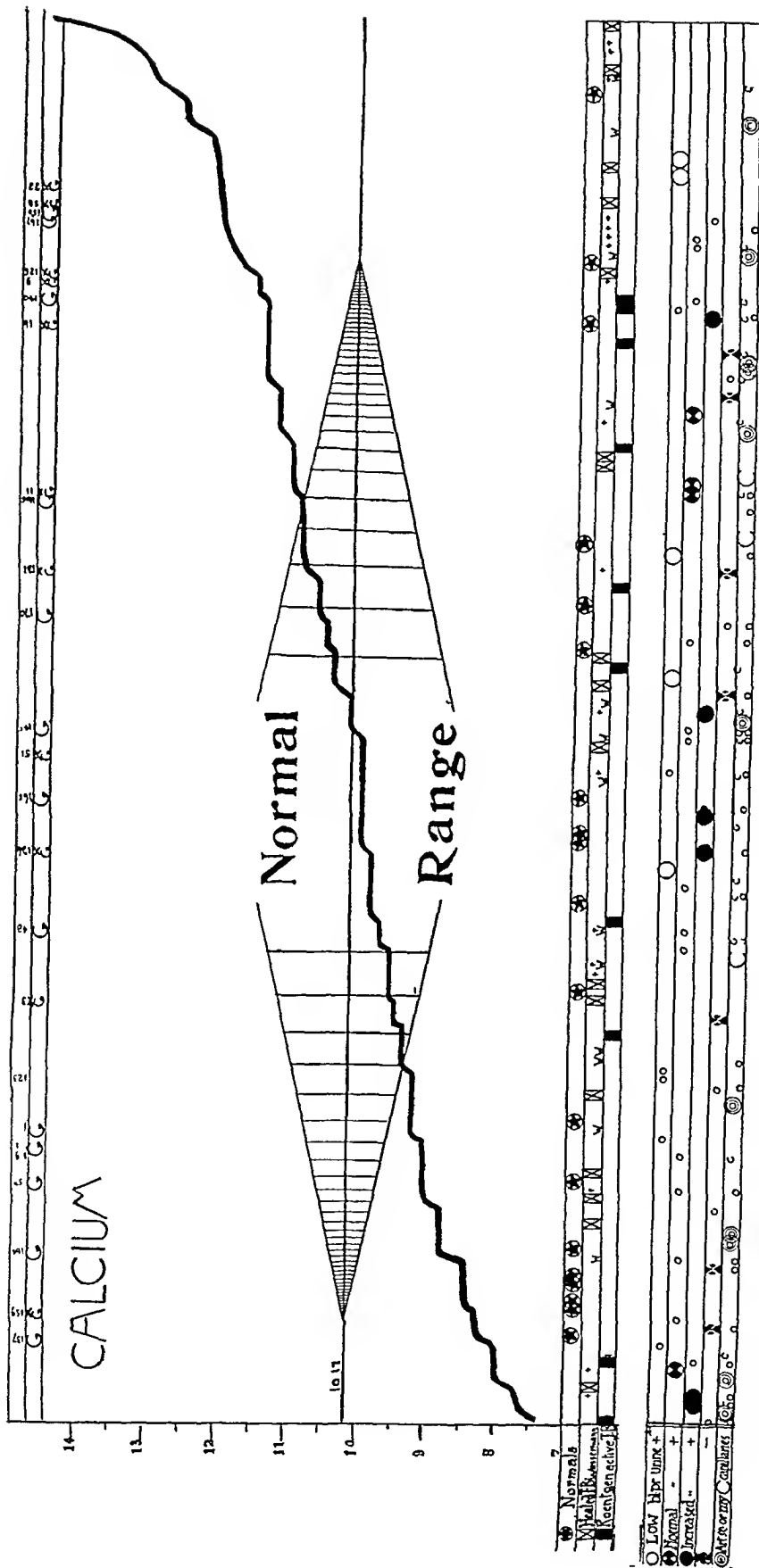


Chart 5 —The calcium level in the serum of normal persons and patients with various clinical conditions

The groups with high levels of calcium include none of the persons having active tuberculosis, but include a number of persons with skin disorders, as well as those with peripheral vascular changes—scleroderma, Raynaud's disease, Buerger's disease, etc. A number of outstandingly sympathetotonic persons are included, but vagotonic types also occur.

In general, the carbon dioxide tension is reduced, the sugar, the skin resistance, the pulse rate, the wheals due to epinephrine and thyroxin and the permeability of the capillaries are increased, the ice reaction time is prolonged, and the blood pressure is lower than in the group with low levels of calcium.

The group with low levels of calcium, on the other hand, includes two persons with active tuberculosis, an increased number of arterio-

TABLE 11—*Comparison of the Averages Obtained for the Groups Showing High Levels and Low Levels of Calcium with the Averages Obtained for the Group of One Hundred Normal Men*

Group	Number in Group	Calcium, Mg	Carbon Dioxide Combining Power	Sugar, Mg	Muscle Reaction	Skin Resistance	Pulse Rate	Ice Reaction Time, Seconds	Intracutaneous Reaction to		Systolic Blood Pres- sure	Diastolic	Permeability of Capillaries
									Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)			
Group with high level of calcium	20	12.7	55.2	75.7	3.2	0.61	80	21	20.2	13.6	120	69	64
Group of "normal" men	100	10.17	57.7	71	3.2	0.46	72	19	19.2	11.2	124	71	62
Group with low level of calcium	20	8.1	56.1	69.7	2.6	0.43	72	19.3	19	12.3	127	71	62.6

sclerotic persons (as proved by roentgen examination), as well as more normal persons. There are, too, apparently more persons of the vagotonic type in this group, thirteen of the twenty giving such a reaction.

Potassium—The highest potassium value, 29.7 mg. per hundred cubic centimeters, is found in a patient with glaucoma, hay-fever and roentgenologic evidence of active tuberculosis, the lowest 13.1 in a person with roentgenologic evidence of active tuberculosis. The range for the actually normal group is from 16.6 to 27.4.

In tables 12, 13 and 14, some of the observations on the group with high levels of potassium (averaging 26.5) are recorded. In table 13, the corresponding observations on the group with low levels of potassium (averaging 15.1) are recorded. For purposes of comparison, table 14 brings together the averages of the groups with the high levels of potassium, the group of 100 "normal" men and the group with low levels of potassium.

TABLE 12—Results of Examinations of the Twenty Persons with the Highest Levels of Potassium

Individual Number	Diagnosis	Potassium, Mg	Carbon Dioxide Combining Power	Sugar, Mg	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Thyroxin, Wheel (Diameter, Mm)	Epinephrine, Wheel (Diameter, Mm)	Blood Pressure		Permeability of Capillaries	Inflammatory Index
140	Glaucoma, tuberculosis, sensitized	29.7	55.6	82		0.45	40	Vagotonic	18	27	100	70	68	4
25	Tuberculosis	28.8	59.8	67	1.2	0.24	20	Sympatheticotonic	21.2	9	140	80	57	9.5
23	Healed tuberculosis	28.6	57.4	85	3	0.42	28	Vagotonic	17.2	7.2	102	58	67	11.1
56	Tuberculosis	28.6	56.6	65	1	0.32	15	Vagotonic	17.2	13.4	124	88	61	10
141	Glaucoma	28.2	64.6	86		0.20	15	Vagotonic	17.4	10	118	78		
34	Changes in capillaries	27.7	56.4	78	2.7	0.59	25	Vagotonic	18	7.2	134	78	56	7.7
48	Syphilis	27.6	58.3	71	1.6	0.10	35	Sympatheticotonic	19.2	8	104	72	66	9.7
50	Normal	27.4	64.9		2.8	0.48	15	Sympatheticotonic	24.8	10.4	128	70	71	8.8
26	Syphilis	26.6	63.4	69	2	0.28	35	Vagotonic	19.6	7.2	92	48	72	11
36	Albuminuria	26.3	57.6	90	2.8	0.11	20	Vagotonic	20.8	7.4	104	50	58	7.2
47	Healed tuberculosis	26.2	56.4	72	5	0.13	15	Vagotonic	21.6	9	136	64	62	12.8
32	Arteriosclerosis	26.1	54.1	76	7.4	0.18	25	Vagotonic	23.6	9.8	144	86	60	10
33	Epilepsy	26.1	54.5	83	2	1.75	12	Sympatheticotonic	20	5.4	122	66	73	10
2	Epilepsy	26.1	55.6	74		0.10		Sympatheticotonic			100	68	69	9.8
58	Exophthalmic goiter	25.9	52.9	120		0.10	26	Vagotonic	19.6	11.2	124	60	75	15
81	Arteriosclerosis, myocarditis	25.3	57	63	2.3	0.10	45	Vagotonic	14	10	144	63	59	10
51	Exophthalmic goiter	25.8	55.5	91	5	0.13		Sympatheticotonic	19.2	9.2	124	50	77	14
5	Nervous	25.7	63.9	72	3.2	0.21		Vagotonic			132	92	72	13
21	Arteriosclerosis	25.6	62.9	72	3.9	0.74	25	Vagotonic	23.2	7.2	140	84	62	9
35	Normal	25.2	57.6	79	1.8	0.38	20	Vagotonic	22.8	9.2	108	78	54	6.7
Averages and totals		26.5	58	75	2.9	0.35	24	14 V, 6 S	20	9.8	121	70	65	10

TABLE 13—The Results of Examinations of the Twenty Persons with the Lowest Levels of Potassium

Individual Number	Diagnosis	Potassium, Mg	Carbon Dioxide Combining Power	Sugar, Mg	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheel (Diameter, Mm)	Thyroxin, Wheel (Diameter, Mm)	Blood Pressure		Permeability of Capillaries	Inflammatory Index
88	Tuberculosis	13.1	58.1	79	2.5	0.63	15	Vagotonic	18.4	12.4	128	76	58	8.1
80	Nervous	13.7	53.2	69	3.8	1.60	30	Vagotonic	14.8	13.4	116	68	91	15.1
146	Myasthenia gravis	14.4	71.06	77		0.55	30	Vagotonic	18	19	120	78	75	5
90	Nervous	14.5	57.9	68		0.44	10	Sympatheticotonic	18.4	6.2	122	54	69	7.6
132	Eczema	15	40.3	67		0.31	10	Vagotonic	18.4	13.4	132	78	68	11.3
62	Aortic regurgitation	15.2	56.8	67	5	0.15	15	Vagotonic	17.2	11.4	140	40	52	8.7
115	Arteriosclerosis	15.2	51.8	60	2	0.23	10	Vagotonic	17.2	14.2	148	84	46	5.7
108	Tuberculosis	15.3	54.1	63	0.6	0.44	18	Sympatheticotonic	18	14.8	94	52	63	8
134	Arteriosclerosis	15.4	54.8	71		0.68	12	Sympatheticotonic	23.6	19.2	148	86	60	4
130	Nephritis	15.5	55.6	86	2	0.35	15	Vagotonic	20	11.2	106		71	4.7
77	Sensitized	15.6	60.6	71	1	1	35	Vagotonic	14	10	126	78	87	10
145	Glaucoma	15.7	55.4	70		0.35	20	Sympatheticotonic	18	16	136	80	67	4.4
86	Nervous	15.9	55	94	1.4	0.36	25	Vagotonic	18.8	15.4	118	60	58	3.8
69	Nervous	16	54.8	70	2	1.90	20	Sympatheticotonic	21.2	14.4	140	48	51	12.7
109	Nervous	16.1	51.4	67		0.47	25	Vagotonic	18	12	106	70	72	12
127	Nephritis	16.2	59.1	81	3	1.20	16	Sympatheticotonic	18.4	15.4	106	76	50	3.8
110	Healed tuberculosis	16.3	57.2	61	2	0.60	30	Vagotonic	20.8	12	110	62	54	7.2
65	Nephritis	16.4	53.1	65	0.4	0.80	13	Sympatheticotonic	15.8	9.2	100	70	61	10
64	Normal (nervous)	16.6	55	52	5	0.22	7	Sympatheticotonic	20	6.4	112	60	66	10
45	Arteriosclerosis	16.6	54.3	77	7.4	0.23	20	Vagotonic	20.4	16.4	162	114	54	9
Averages and totals		15.1	55.2	70	2.7	0.63	18.5	11 V, 8 S	18.4	13.1	123	70	63	8

In the group with the higher levels are three patients with roentgenologic evidence of active tuberculosis, two with syphilis, two with glaucoma and two with epilepsy. The reaction to epinephrine is predominantly vagotonic. The group with the low levels includes the "nervous" persons. In this group eleven react vagotonically.

As compared with the group having low levels of potassium the group having the high levels reveals higher CO_2 combining power, more sugar, larger wheals due to epinephrine, smaller wheals due to thyroxin and a higher inflammatory index. The reaction to ice is delayed.

TABLE 14—Comparison of the Averages Found for the Groups with High and Low Levels of Potassium with the Averages Found for the Group of One Hundred "Normal" Men

	Number in Group	Potassium, Mg	Carbon Dioxide Combining Power	Sugar, Mg	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure Systolic Diastolic		Permeability of Capillaries	Inflammatory Index
Group with high level of potassium	20	26.5	58	75	2.9	0.35	24	14.2	20	9.8	121	70	65	10
Group of "nor- mal" men	100	20.4	57.7	71	3.2	0.46	19		19.2	11.2	124	71	62	8.2
Group with low level of potassium	20	15.1	55.2	70	2.7	0.63	18.5	11.2	18.4	13.1	123	70	63	8

SUMMARY AND CONCLUSIONS

An examination was made of the serum calcium and potassium of 100 so-called normal persons. Of this group, twenty were regarded as actually normal on careful examination.

The K/Ca ratio from 1.7 to 2.4 we regard as normal. Persons with roentgenologic evidence of active tuberculosis are at the extreme ends of the scale. Those with vascular changes in addition to the tuberculosis have the higher ratios. Among abnormal persons, glaucoma and exophthalmic goiter produce no marked deviations from normal. "Nervous" persons have low ratios.

The normal calcium range was found to be from 8.2 to 12.7. In the group with the high range are the persons with diseases of the skin, as well as those with peripheral vascular disturbances, such as scleroderma, Buerger's disease, Raynaud's disease, etc. These persons tend toward the sympatheticotonic type.

The normal potassium range extended from 16.6 to 27.4. The group with low levels of potassium includes the "nervous" persons.

TOTAL PROTEINS

Serum proteins for the normal as well as abnormal groups varied from a low of 6.33 per cent in patient 86 (nervous) to a high reading of 9.87 per cent in a case of so-called Buerger's disease (syphilitic). For the strictly normal group, the range was from 7.5 to 8.5 per cent. Patient 17, classified as normal, but with an abnormal K/Ca ratio, etc.,

TABLE 15—*The Results of Examinations of the Twenty Persons with the Lowest Concentrations of Protein*

Individual Number	Protein, Mg	Diagnosis	CO ₂ Combining Power	Weight/Length Ratio	Basal Metabolic Rate
86	6.33	Nervous	55	176	6.4
145	6.55	Glaucoma, syphilis	55.4	166	19
85	6.65	Fever, unknown origin	56.9	187	18.8
140	6.77	Tuberculosis, glaucoma	55.6		
60	6.87	Cardiovascular renal condition	56.6	229	
116	7	Urticaria	65.1	195	9
67	7	Dwarf	56.9	195	32
118	7	Tuberculosis, arthritis	54.2	154	-11
77	7	Sensitized	60.6	187	7.9
30	7.07	Arteriosclerosis	62.5	175	-6
139	7.10	Urticaria	50	176	5
123	7.16	Carcinoma of thyroid	52.4	263	48
110	7.20	Healed tuberculosis	57.2	190	49
11	7.20	Exophthalmic goiter	58.1	195	42
24	7.20	Healed tuberculosis	53.7	219	1
101	7.20	Eczema	57.4	191	31
92	7.20	Nervous	56.8	210	-1
96	7.26	Cardiovascular renal condition	53.4	243	31
132	7.30	Eczema	40.3	234	-1.2
161	7.30	Glaucoma	49.4	171	+16

TABLE 16—*The Results of Examinations of the Twenty Persons with the Highest Concentrations of Protein*

Individual Number	Protein, Mg	Diagnosis	CO ₂ Combining Power	Weight/Length Ratio	Basal Metabolic Rate
169	9.87	Buerger's disease	55.1		+7
164	9.56	Glaucoma syphilis	55.6	223	-4.7
136	9.25	Pellagra	57.9	180	20
75	9.23	Cardiovascular renal condition	61.6	243	+2.5
56	9.14	Tuberculosis	56.6	247	-17.9
125	9.13	Exophthalmic goiter	55.5	197	59
170	8.92	Glaucoma	52.5	170	+33
5	8.92	Neurosis	6.39	210	
32	8.80	Cardiovascular renal condition	54.1	190	+22
146	8.80	Myasthenia	71.06	192	+1.8
79	7.87	Ulcer	57	220	-15.2
17	8.72	Normal (?)	59.1	216	-11
167	8.71	Glaucoma, arteriosclerosis	47.9	158	-13
117	8.71	Arthritis syphilis	52.4	195	-7
40	8.71	Changes in capillaries	55.7	201	22
154	8.71	Glaucoma	56.6	181	18
10	8.70	Healed tuberculosis	59.4	230	-12.4
68	8.66	Healed tuberculosis	51.1	217	25.8
121	8.66	Arthritis deformans	56.8	294	11
66	8.66	Cardiovascular renal condition	53.1	257	1.3

is again unusual in having a somewhat higher protein concentration, 8.75 per cent. We do not regard this as normal. The twenty persons with the lowest concentrations of the entire series are tabulated in table 15 (average, 7 per cent).

The twenty persons with the highest concentrations are presented in table 16 (average 8.9).

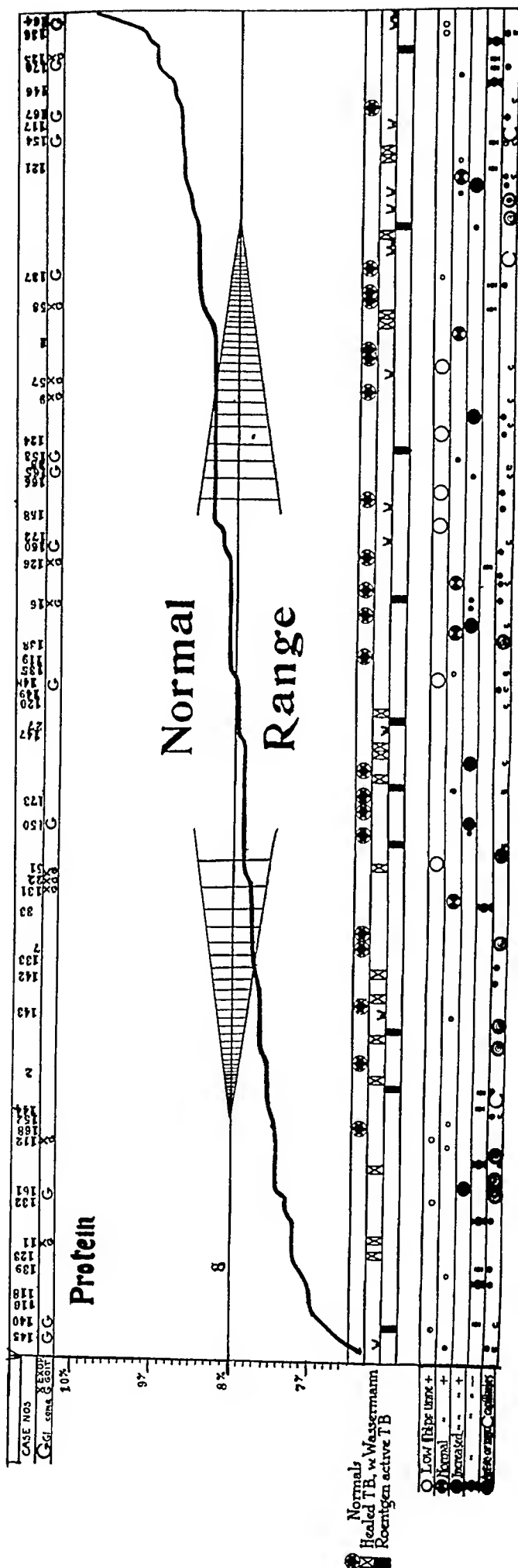


Chart 6.—The amount of protein in the serum of normal persons and patients with various clinical conditions

A table of comparison with the normal is given in table 17. There are no obvious correlations other than those indicated, and these are by no means striking. A graphic presentation has been prepared in chart 6.

TABLE 17—*Comparison of the Averages Found for the Groups with High and Low Concentrations of Protein with Those Found for the One Hundred "Normal" Men*

Group	CO ₂ Combining Power	Weight/ Length Ratio	Basal Metabolic Rate
Group with low level of protein	54.8	197	+15
Group of 100 "normal" men	57.7	217	+8
Group with high level of protein	57.1	210	+6

In general it will be observed that in the group of 100 "normal" persons, both active and inactive tuberculosis revealed by the x-rays is scattered over the entire range. The cases in which there were cardiovascular renal disturbances more frequently showed the higher concentrations. This is true of the cases in which glaucoma is present as well.

GLOBULINS

The range of globulins for the entire series is from 0 to 90 per cent. For the actually normal persons, the range is approximately from 20 to 45 per cent (with an albumin/globulin ratio of from 5 to 1.2). It may be noted from the curve in chart 7 that two normal persons (nos. 17

TABLE 18—*The Results of Examinations of the Twenty Persons with the Lowest Amounts of Globulin*

Individual Num- ber	Glob- ulin	Diagnosis	Reaction to Epinephrine		Reaction to Thyroxine	
			Wheal, Diameter, Mm.	Flare, Radius, Mm.	Wheal, Diameter, Mm.	Flare, Radius, Mm.
149	0	Nervous	20	9.7	19	0
153	0	Edema, glaucoma, nephritis	22	6.5	18	0
144	2	Arteriosclerosis, pellagra, changes in capillaries	14.4	11.5	15	0
154	3	Arteriosclerosis, glaucoma, changes in capillaries	23	10	26	0
173	6	Cord tumor	21	12.5	18	0
166	8	Eosinophilia	17	11.5	18	0
138	11	Frohlich's syndrome (?)	23	9.5	17	6.5
168	13	Orthostatic albuminuria	18	16	14	0
150	15	Glaucoma	17	14	16	0
165	16	Glaucoma	16.8	13	12.5	0
17	17	Normal	20.6	10.2	20.6	10.4
49	17	Cardiovascular renal condition	12.4	10.2	4.2	1
158	17	Hodgkin's disease	19.2	11.3	23	0
59	17	Normal	22	7.2	15.6	8
139	18	Urticaria	16	11	14	12.5
25	19	Tuberculosis (x-ray evidence)	21.2	12.2	9	15.2
142	19	Tumor of the brain	18.6	8.7	17	0
169	20	Buerger's disease	20.8	11	18	0
164	20	Glaucoma	18	14.7		
21	20	Cardiovascular renal condition	23.2	12.6	7.2	2.6

and 59) are slightly below and three (nos 41, 29 and 43) are at the upper margin. Of these persons, no 17 has been noted previously because of his deviations, of the three with high globulin, no 29 has a trace of bile in the urine and no 43 a decrease in the number of the capillaries of the skin.

TABLE 19—*The Results of Examinations of the Twenty Persons with the Highest Amounts of Globulin*

Individual Number	Globulin	Diagnosis	Reaction to Epinephrine		Reaction to Thyroxin Wheal, Diameter, Mm
			Wheal, Diameter, Mm	Flare, Radius, Mm	
133	90	Scleroderma			
115	60	Cardiovascular renal condition	17.2	6.2	14.2
130	60	Cardiovascular renal condition, arteriosclerosis	20	5.4	14.2
24	60	Healed tuberculosis	16.8	12.6	6.6
102	55	Tuberculosis	23.2	7.4	12.2
128	55	Cardiovascular renal condition, sensitized			11.4
145	55	Glaucoma, Wassermann reaction +	18	13.6	16
27	52	Lead poisoning, Wassermann reaction +			
42	50	Cardiovascular renal condition, myocarditis	19.2	11.8	9.2
43	50	Normal	22	7.1	10
108	50	Tuberculosis	18	2.4	14.8
84	50	Cardiovascular renal condition	16.1	8.1	10.1
120	50	Purpura	21.2	7.2	12.1
29	50	Normal	22.8	9.8	7.2
41	50	Normal	24	13.2	6.2
79	50	Ulcer	19.2	9.4	8.2
101	45	Sensitized	19.6	7	10
104	45	Tuberculosis	20.8	6.2	12
33	45	Epileptic	20	12.6	5.4
100	45	Healed tuberculosis	18.8	8.6	12

TABLE 20—*A Comparison of the Averages Obtained for the Groups Showing Low and High Values of Globulin*

Group	Globulin, %	Reaction to Epinephrine		Reaction to Thyroxin Wheal, Diameter, Mm
		Wheal, Diameter, Mm	Flare, Radius, Mm	
Group with low level of globulin	12	19.2	11.3	16
Group with high level of globulin	50	18.7	8.3	10.6

In chart 7, it may be observed that the persons with cardiovascular renal lesions tend to accumulate at the high end of the scale of the globulin, as do the patients with active tuberculosis.

In table 18, we have tabulated the results of some examinations of the twenty persons with the lowest values of globulin and in table 19 of those with the highest values. In the latter group, it is of interest to note that the patient with generalized scleroderma had the highest amount.

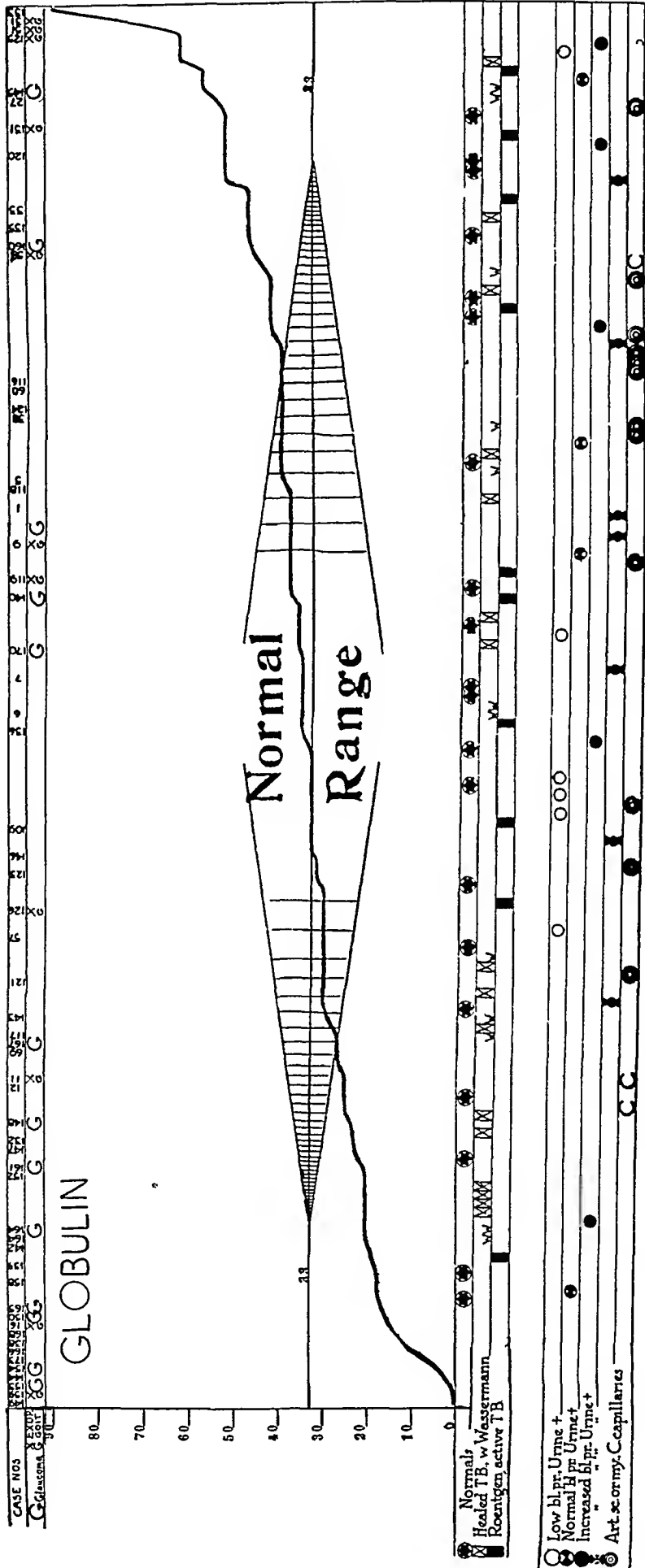


Chart 7 —The amount of globulin in the serum of normal persons and patients with various clinical conditions

KROMAYER ERYTHEMA TIME

When the skin of the forearm is exposed directly to the light of the Kromayer lamp for thirty seconds, and the time from the beginning of the exposure to the appearance of the erythema determined, a considerable variation in the time, as well as in the intensity of the response, is found

TABLE 21—*The Results of Examinations of the Twenty Persons Showing the Most Rapid Reactions to Kromayer Light*

Individual Number	Diagnosis	Blister Time, Hr	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm	Thyroxin, Wheal, Mm	Pigmentation of Skin*	Color of Hair	Kromayer Light Erythema Time, Hr	CO ₂ Combining Power
45	Cardiovascular renal condition	6	54	9	20	Vagotonic	20.4	16.4	5	Dark brown	3/4	54.3
116	Urticaria	3.5	60	17	9	Vagotonic	20.4	5	4	Brown	1/2	55.1
66	Cardiovascular renal condition, arterio sclerosis, myocarditis	6	78	13	1.3	Sympathetico tonic	20	10.2	3.5	Light brown	5/6	53.1
33	Epilepsy	7.5	73	10	-18	Sympathetico tonic	20	5.4	3	Dark brown	1	54.5
100	Healed tuberculosis	6	53	9	-1.6	Vagotonic	18.8	12	3	Blond	1	53.3
152	Angioneuritic edema, sensitized	4	73	18	4.8	Vagotonic	26	9	3	Dark brown	1	63.4
153	Hodgkin's disease	15	61	4	+37	Sympathetico tonic	19.2	28		Dark brown	1	57.8
142	Tumor of the brain	7	54	7.7	+0.5	Sympathetico tonic	18.6	17	5	Dark brown	1	59
168	Orthostatic albuminuria	6	75	12	-9	Vagotonic	18	14		Brown	1	55.6
117	Syphilitic arthritis	6	61	10	-7	Sympathetico tonic	19.2	20	5	Dark brown	1	52.4
60	Cardiovascular renal condition	8			0	Sympathetico tonic	19.2	21	4.5	Light brown	1	56.6
149	Nervous	10	54	5.4	+5	Vagotonic	20	19	4	Dark brown	1	65.4
7	Cardiovascular renal condition	6	70	11.6	+7	Vagotonic	19.2	15.4	4.5	Light brown	1 11/10	57.9
46	Inanition	6	59	10	+13	Sympathetico tonic	21.2	12.2			1 1/6	56.2
160	Asthma, glaucoma	15	66	4.4	+16	Vagotonic	16	20			1 1/6	62.7
112	Cardiovascular renal condition	6	54	9	+19.6	Vagotonic	22.4	9.8	4	Dark brown	1 1/6	59
111	Cardiovascular renal condition	6	57	9.5	+31	Sympathetico tonic	22	10.8	5	Dark brown	1 1/6	55.3
120	Purpura	6	82	13	-5	Sympathetico tonic	21.2	12.1			1 1/5	52.2
48	Syphilis	6.75	66	9.7	+8	Sympathetico tonic	19.2	8			1 1/4	58.3
32	Cardiovascular renal condition	6	60	10	+22	Vagotonic	23.6	9.8	3.5	Brown	1 1/4	54.1

* Indicated on a scale of 1 to 10, 1 being white and 10 "light negro"

Investigators have previously determined that in the white race, the reaction is influenced by, but does not wholly depend on, the degree of pigmentation of the skin. It is known that constitutional factors play a rôle, and in the most practical field, i. e., the treatment of tuberculosis by light, it is common knowledge that a patient who does not react promptly and with production of pigment usually is not benefited by irradiation.

TABLE 22—*The Results of Examinations of the Twenty Persons with the Slowest Reactions to Kromayer Light*

Individual Number	Diagnosis	Blister Time, Hr	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm	Thyroxin, Wheal, Mm	Pigmentation of Skin	Color of Hair	Kromayer Light Erythema Time, Hr	CO ₂ Combining Power
133	Scleroderma				2	Sympatheticotonic			5	Black	Did not appear	50.2
34	Changes in capillaries	7.25	56	7.7	13.6	Vagotonic	18	7.2	3.5	Black	8	56.4
49	Cardiovascular renal condition	6	66	11	7.1	Sympatheticotonic	12.4	4.2	3.5	Dark brown	5½	59.1
1	Nervous	8	68	8.5	7	Sympatheticotonic	20	13.2	4	Brown	5	62.1
63	Cardiovascular renal condition, arterio sclerosis	7.5	71	9.4	0.65	Vagotonic	20	12.2	4	Dark brown	5	62.4
99	Healed tuberculosis	9	73	8.1	—3	Vagotonic	20.4	12.2	3.5	Blond	4½	57.4
107	Myocarditis, arterio sclerosis, cardiovascular renal condition	9	58	6.4	—65	Vagotonic	20.8	13.4	4	Light brown	4	55.2
127	Cardiovascular renal condition	13	50	3.8	—35	Sympatheticotonic	18.4	15.4	6	Brown	4	59.1
77	Sensitized	9	87	10	+7.9	Vagotonic	14	10	3	Dark brown	4	60.6
79	Ulcer (cardiovascular renal condition)	15	86	5.7	—15.2	Sympatheticotonic	19.2	8.2	2.5	Black	4	57
123	Cardiovascular renal condition, sensitized	15	58	3.8	—18	Sympatheticotonic		14.4	6	Dark brown	4	58.1
110	Healed tuberculosis	7.5	54	7.2		Vagotonic	20.8	12	4	Blond	4	57.2
2	Epilepsy	7	69	9.8	—11	Sympatheticotonic			4	Blond	3½	55.6
78	Normal	7	86	12	—0.62	Sympatheticotonic	19.6	12.4	3.5	Light brown	3¾	62.7
18	Healed tuberculosis	8	70	8.7	+4.2	Vagotonic			3	Brown	3¾	58.4
29	Normal (bile pigment in urine)	6.5	70	10.7	3.5	Sympatheticotonic	22.8	7.2	4.5	Dark brown	3¾	60.1
50	Normal	8	71	8.8	21	Sympatheticotonic	24.8	10.4	4	Light brown	3	61.9
85	Fever, unknown origin	6	56	9.3	+18.8	Vagotonic	17.2	14.2	2	Dark brown	3	56.9
75	Cardiovascular renal condition	9	60	6.6	+2.5	Vagotonic	20.4	10	5.5	Dark brown	3	61.6
65	Cardiovascular renal condition	6	61	10	+2.9	Sympatheticotonic	15.8	9.2	2.5	Blond	3	53.1

TABLE 23—*A Comparison of the Averages Obtained for the Groups with Fast and Slow Kromayer Lamp Erythema Times with Those Obtained for the Group of One Hundred "Normal" Men*

Group	Kromayer Light Erythema Time, Hr	Blister Time, Hr	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Epinephrine, Wheal, Mm	Thyroxin, Wheal, Mm	Pigmentation of Skin	CO ₂ Combining Power
Group with short erythema time	1	7.1	65	10	+7	20	13.8	4	56
Group of 100 "normal" men	2	7.5	62	8.2	+8	19.2	11.2		57.7
Group with long erythema time	3	8.5	66	8.3	+3	19	10.9	4	58.4

In our series of cases, we have roughly estimated the pigment content of the skin in each case by comparing it with a series of filter papers stained with varying dilutions of Bismarck brown. A scale from 1 to 10 was used, 1 being white and 10 approximating the color of the skin of a light negro.

The color of the hair was noted as blond, black, dark brown, light brown and brown.

During the course of our examination of 100 so-called normal persons, it was shown that the prolongation of the erythema time was associated with a longer blister time, a lowering of the inflammatory index, a low basal metabolic rate, high CO_2 combining power and a lessened wheal due to epinephrine.

When we examine the group of 100 and the clinical material, as well, we find that the shortest time (45 minutes) was noted in patient 45, a man 39 years of age, with a vagotonic reaction to epinephrine and a history of urticaria twenty years previously. His blood pressure is 162 systolic and 114 diastolic (when 4 years of age, he had scarlet fever with involvement of the kidneys). The pigmentation of the skin is 5, and the hair dark brown.

On the other hand, two persons did not react at all. One had scleroderma, the other had an exophthalmic goiter, and had a fairly dark skin (pigment 6) and dark brown hair.

Our truly normal group had a range of erythema time from 75 to 195 minutes.

We have grouped the twenty persons with the shortest erythema times (average 1 hour) in table 21, and we present the twenty with the longest erythema times in table 22. For purposes of comparison, in table 23, we include with the averages for these two groups the averages for the 100 so-called normal men.

It appears that pigmentation, as such, plays comparatively little rôle in the relative rapidity or delay in the appearance of the Kromayer light erythema. Other factors with which the inflammatory index seems associated are probably of more importance. The CO_2 combining power and the endocrine status, particularly a difference in the wheals due to thyroxin are, perhaps, concerned.

Blondness per se is not important. In the group showing delayed reactions, we find four blonds and in the group showing rapidity, none at all.

BASAL METABOLIC RATE

In the introduction, we pointed out that determinations of the basal metabolic rate on a group of nonhospitalized workmen without a possibility of recheck affords a most unsatisfactory examination. We were, however, forced to accept this condition for our group of 100 "normal" men. Our average of $+8$ is evidence of a lack of absolute rest,

TABLE 24—The Results of Examinations of the Twenty Persons with the Lowest Basal Metabolic Rates

Individual Number	Basal Metabolic Rate	Diagnosis	Blister Time, Hr	Permeability Ratio	Calcium, Mlg	Potassium, Mlg	K / Ca Ratio	Kromayer Light Ery- thema Time, Min	Skin Resistance	Pulse Rate	Epinephrine, % Increase	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Weight/Length Ratio
37*	-21.4	Normal	9	53	10	22.6	2.26	90	0.31	18	—	Vagotonic	20.4	21.6	10	0	251
13*	-22	Healed tuberculosis	8	64	9.6	23.8	2.48	150	0.89	72	+24	Sympathetotonic	17.6	6.8	22.6	9.2	223
33	-18	Epilepsy	7.5	73	9.5	26.1	2.73	60	1.75	76	+2	Sympathetotonic	20	12.6	5.1	0	210
123*	-18	Cardiovascular renal condition	15	58	10.2	19.7	1.93	210	1	84	+13	Sympathetotonic	17.2	5.8	13	7.1	217
56*	-18	Tuberculosis	6	61	9.8	28.6	2.82	135	0.32	80	+14	Vagotonic	17.2	5.8	13	7.1	217
79*	-15.2	Ulcer	15	86	11.2	20	1.78	240	0.71	76	+8	Sympathetotonic	19.2	9.4	8.2	12.2	220
107	-13	Glaucoma	15	55	12	22.7	1.9	120	0.85	84	+62	Sympathetotonic	17	11.2	15	0	158
118	-11	Tuberculosis (?), arthritis	10	87	12.2	17.2	1.4	110	1.9	72	—	Vagotonic	16.8	7.4	12	8.6	151
17*	-11	Normal	8	66	12.7	19.2	1.43	90	0.22	66	0	Vagotonic	20.8	10.2	20.6	10.4	216
2	-11	Epilepsy	7	69	12.9	26.1	2.02	210	0.1	100	+64	Sympathetotonic	18	16	14	0	215
108	-9	Orthostatic albuminuria	6	75	9.10	17.6	1.88	60	0.16	80	+4	Vagotonic	18.1	11.6	6.2	0	192
96*	-8	Nervous	9	69	11.1	14.5	1.34	105	0.44	67	+17	Sympathetotonic	20.4	9.8	14	0	197
8*	-8	Normal	10	64	10.5	21	2	120	0.48	60	+90	Sympathetotonic	20	7.8	12	9	189
122*	-7.3	Normal	4	68	10.6	19.2	1.81	75	0.37	68	—	Vagotonic	17	11.5	18	0	200
166	-7	Leishmaniasis	7	57	9.1	20.66	2.27	75	0.08	96	—	Vagotonic	19.2	6.2	20	0	195
117	-7	Syphilitic arthritis	6	61	9.2	17.5	1.8	60	0.25	78	6	Sympathetotonic	17.2	9.2	13.4	11	258
83*	-7	Normal	9	51	8.2	19	2.31	90	0.16	60	+10	Vagotonic	19.6	7	11.2	0	243
106*	-6.6	Cardiovascular renal condition	6	71	11.2	19	1.69	90	0.63	84	—2	Vagotonic	19.6	12.2	6.4	0	224
3*	-6.5	Healed tuberculosis	6.5	67	11.1	16.7	1.47	90	0.33	65	+8	Vagotonic	20.8	5.8	13.1	6.2	265
107*	-6.5	Cardiovascular renal condition	9	58	8.1	18.4	2.3	255	0.33	72	—1	Vagotonic	20.8	5.8	13.1	6.2	265
11 72	Aver ages and totals		8.65	65.8	10.41	20.4	1.93	125	0.565	76.2	+15	11 V, 9 S	18.8	10.2	12.6	3.8	214

* One of group of 100 "normal" men

TABLE 25—The Results of Examinations of the Twenty Persons with the Highest Basal Metabolic Rates

Individual Number	Basal Metabolic Rate	Diagnosis	Blister Time, Hr	Permeability Ratio	Calcium, Mg	Potassium, Mg	K / Ca Ratio	Skin Resistance	Pulse Rate	Epinephrine, % Increase	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Min	Epinephrine, Flare, Min	Weight/Length Ratio	Kilometer per Light Dry-thenna Time, Min	
126	+105	Exophthalmic goiter	6		9.8	18	1.83	0.20	96	+20	Sympatheticotonic	19.6	7	12	0	174
131	+88	Exophthalmic goiter	5	77	10.6	18	1.7	0.21				16.8	6.2	10.4	6.2	177
31	+73	Exophthalmic goiter	5.5	70	9.5				114			21.6	7	7.2	0	200
51	+67	Exophthalmic goiter	5.5	77	10	23.8	2.58	0.13	104	+25	Sympatheticotonic	19.2	6.2	9.2	4.8	195
125	+59	Exophthalmic goiter	6	74	11.51			0.18	140			20.4	7	15.2	16.4	197
88*	+54.6	Tuberculosis	7.25	58	9.4	13.1	1.4	0.68	76	-10	Vagotonic	18.4	11	12.4	12	203
9	+49	Exophthalmic goiter	5.5	71	11.5	23.5	2.04	0.75	96	+28	Sympatheticotonic	20.8	12	12	9.4	190
110*	+48.8	Healed tuberculosis	7.5	54	12.1	16.3	1.34	0.60	84	-4	Vagotonic	20	6.8	10	12.2	263
123	+48	Carcinoma of thyroid	9.25	74	9.2	20	2.7		80	-3	Sympatheticotonic	25	9	12	0	181
150	+46	Exophthalmic goiter	5	69	8.23	17.9	2.17	0.22	76	+17	Sympatheticotonic	26.4	10	5	1	233
22	+44	Exophthalmic goiter	6	73	12.1	19.2	1.5	0.17	92	+31	Sympatheticotonic	19.6	10.4	11.2	6.8	188
58	+43.1	Exophthalmic goiter	5	75	12	27.9	2.15	0.10	127	+2	Sympatheticotonic	17	14	16	0	238
11	+42	Exophthalmic goiter	5	70	10.9	24.1	2.21	0.14	108	+06	Sympatheticotonic	19.2	11.3	23	0	173
150	+39	Glaucoma	15	58	12	21.3	1.78	0.22	84	+6	Sympatheticotonic	11	6.2	10	0	209
158	+37	Hodgkin's disease	15	61	9.33	18.53	2	0.29	93	+10	Sympatheticotonic	21.6	5.2	9	0	260
81*	+34.8	Cardiovascular renal condition	6	59	8.4	25.8	3.07	0.10	76	+4	Vagotonic	24	5	12	7	266
47*	+34	Healed tuberculosis	5	62	10.4	26.2	2.51	0.13	70	-5	Vagotonic	17.2	9	13.6	0	195
119	+34	Adenoma of thyroid	6.45	58	9	18.7	2.1	0.08	96	+13	Sympatheticotonic					
170	+33	Glaucoma	15	72	10.58	23.71	2.2	0.07	104							
67*	+32	Dwarf	6	71	8.8	17.6	2	0.19	75	+8	Vagotonic					
		Averages and totals	7.3	67.5	9.81	20.7	2.07	0.23	94.1	+8	10 S, 5 V	20	7.9	12	4.9	205
	50.5															105.7

* One of group of 100 "normal" men

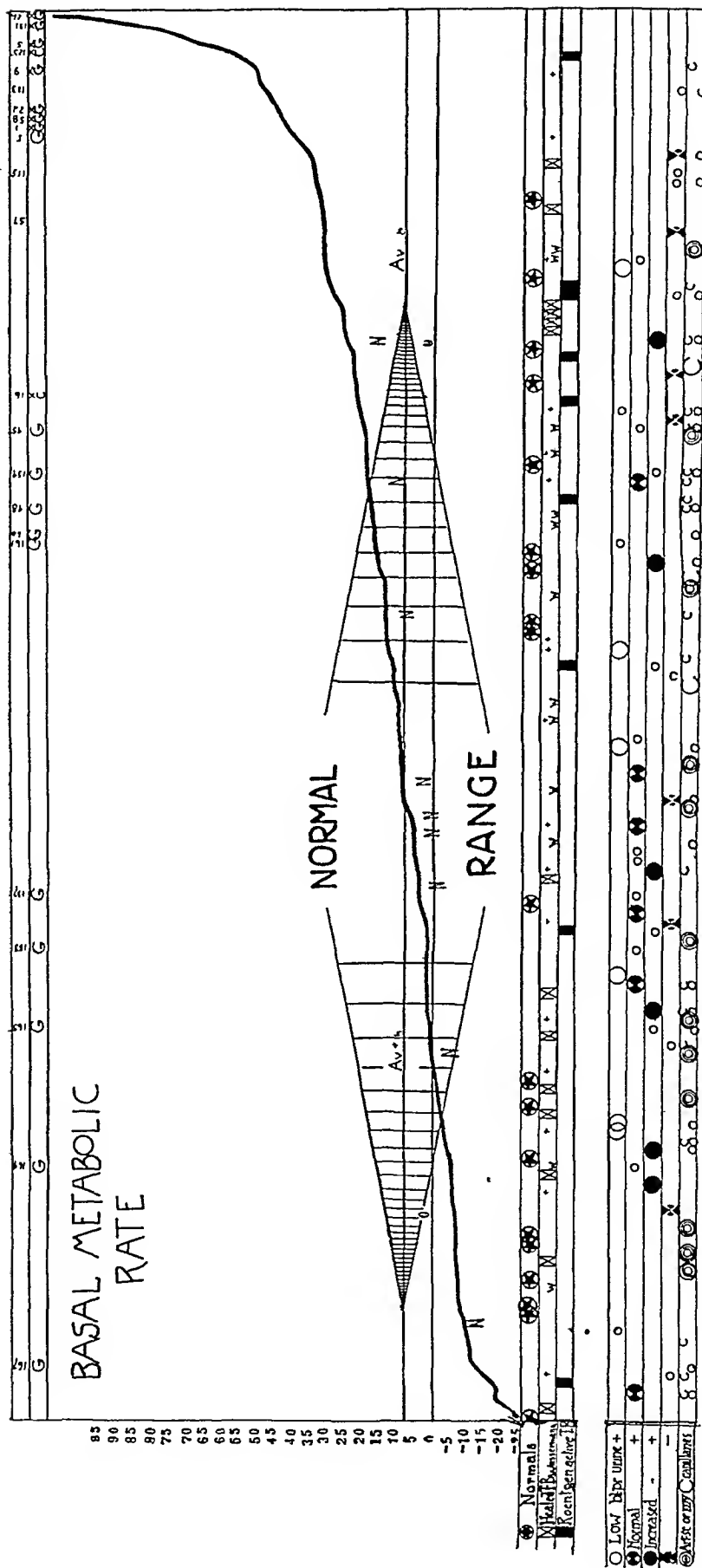


Chart 8—The basal metabolic rate of normal persons and patients with various clinical conditions

and the probability exists that, in some cases, food or stimulants had been taken in the morning before the examination

We have prepared two tables, one including those persons with low basal rates (table 24) and a second including those with extremely high rates (table 25). In this latter table, we have retained the results of the examinations of persons with exophthalmic goiter, contrary to the practice followed in the other tables of results. It will be noted that those with low rates have longer blister times, higher levels of calcium and lower K/Ca ratios, longer Kromayer reaction times and greater skin resistance. They have slower pulse rates and are slightly heavier. The subcutaneous injection of epinephrine hydrochloride shows that, as far as the effect on pulse pressure is concerned, the group with the low ratios has an increase of +15 per cent as compared with +8 per cent of the group with the high ratios, but that there are more sympatheticotonic types in the latter group. The intracutaneous injections indicate that the group with the high ratios has smaller flares due to epinephrine and larger flares due to thyroxin.

Examination of chart 8 indicates that the group with roentgenologic evidence of active tuberculosis has higher rates. There is no apparent connection with the cardiovascular renal condition.

RESISTANCE OF THE SKIN TO ELECTRIC CURRENT

The resistance of the skin to electric current varies from a "low" of 0.07 megohms to a "high" of 6.1. The average for the entire group of 100 "normal" men is 0.46.

For the actually normal persons, the range is approximately from 0.15 to 0.45 (average 0.33). Two of our normal group fall outside these limits, patients 29 and 78. These persons have repeatedly been found at the extremes or beyond the normal range, patient 29 being the one in whom a trace of bile was found in the urine.

In table 26, the results of examinations of the ten persons with the lowest skin resistance are tabulated, and in table 27, those of the ten persons with the highest resistance.

Chart 9 shows the curve of the skin resistance. It will be noted that the majority of the persons with roentgenologic evidence of active tuberculosis are on the side of low resistance. There appears to be nothing characteristic about the persons with cardiovascular renal conditions, the persons with glaucoma are scattered over the entire range. On the other hand, the persons with exophthalmic goiter appear to be on the side of low resistance.

TABLE 26—*The Results of Examinations of the Ten Persons with the Lowest Resistance of the Skin to Electric Current*

Individual Number	Skin Resistance	Diagnosis	Permeability of Capillaries	Basal Metabolic Rate	Weight/Length Ratio	Vascular Reaction to β -pinephrine	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
138	0.07	Frohlich's syndrome	73	+8	270	Vagotonic	23	9.5	17	6.5
170	0.07	Glaucoma	72	+33	170					
172	0.08	Syphilis, Ravnud's disease	72	+18	166	Sympatheticotonic	22.4	16	18	16
166	0.08	Eosinophilia	57	—7	200	Vagotonic	17	11.5	18	0
28	0.08	Healed tuberculosis	64	+24.5	200	Sympatheticotonic	20	12.2	7.4	0
104	0.08	Tuberculosis	54	+27.5	235	Vagotonic	20.8	6.2	12	0
154	0.09	Glaucoma, arteriosclerosis	60	+18	181		23	10	26	0
173	0.09	Tumor of the cord	57	+12	177	Sympatheticotonic	21	12.5	18	0
105	0.09	Healed tuberculosis	62	+31.6	194	Vagotonic	19.6	5.6	12	10.4
135	0.09	Nervous	84	+17	183	Vagotonic	12.4	3.2	20	0
	0.07	Averages	65.5	18.26	197		20	9.5	16.5	

TABLE 27—*The Results of Examinations of the Ten Persons with the Highest Resistance of the Skin to Electric Current*

Individual Number	Skin Resistance	Diagnosis	Permeability of Capillaries	Basal Metabolic Rate	Weight/Length Ratio	Vascular Reaction to β -pinephrine	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
27	6.1	Lead poisoning, syphilis	82	+17	217					
112	2.7	Arteriosclerosis, cardiovascular renal condition	54	+19.6	218	Vagotonic	22.4	7.2	9.8	0
73	2.0	Syphilis	69	+16.3	191	Vagotonic	17.6	8.2	15.6	0
118	1.9	Tuberculosis, arthritis	87	—11	154	Vagotonic	16.8	7.4	12	8.6
137	1.9	Glaucoma	61	+3.6	166	Vagotonic	15.4	10.5	13	0
69	1.9	Nervous, ulcer	51	+4	160	Sympatheticotonic	21	10	14.4	10.2
33	1.8	Epilepsy	73	—18	240	Sympatheticotonic	20	12.6	5.4	0
46	1.7	Inanition	59	+13	168	Sympatheticotonic	21.2	13.2	12.2	11.2
80	1.6	Nervous	91	+13	212	Vagotonic	14.8	12.4	13.4	9.2
161	1.4	Nervous, glaucoma	72	—16	171	Sympatheticotonic	14	13	13	0
	2.3	Averages	69.9	7.4	189.7		18	10.5	12	

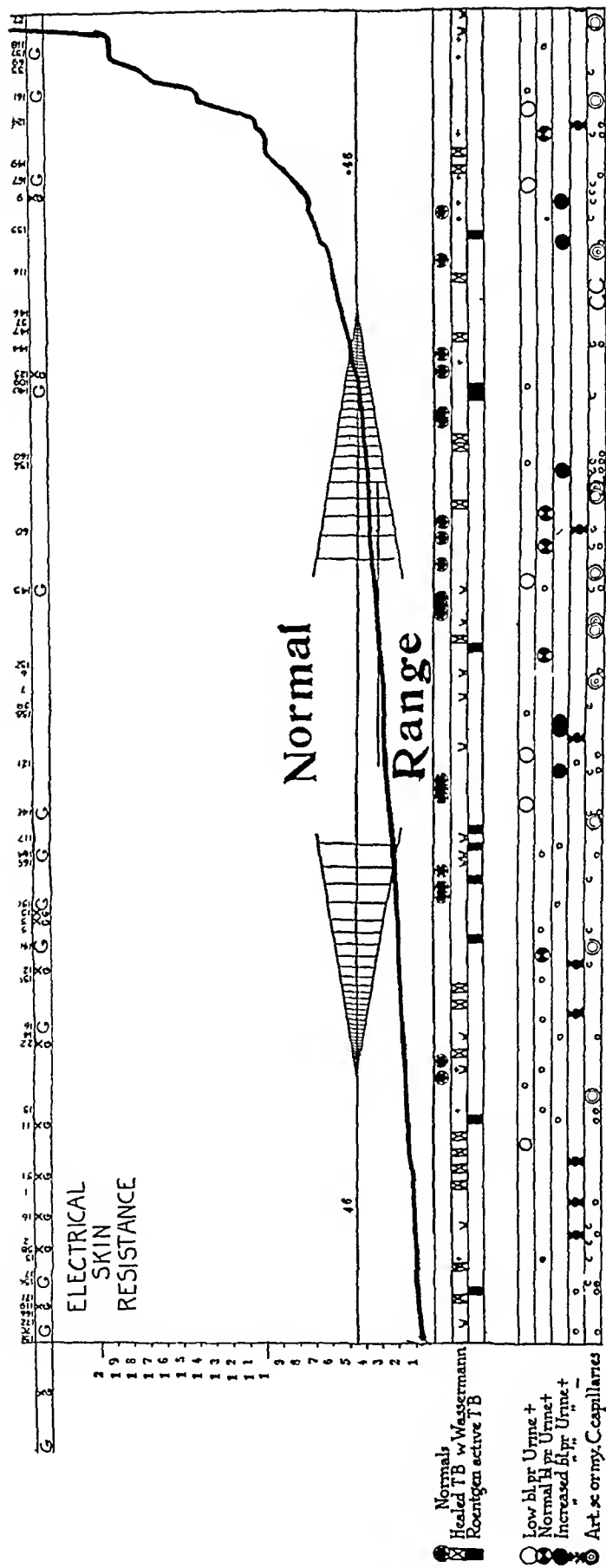


Chart 9—The resistance of the skin to electric current of normal persons and patients with various clinical conditions

MUSCLE REACTIVITY

Hopman¹⁰ has sought to establish the fact that the muscle irritability may be used as a criterion of the autonomic status of a person at the time of examination. In general, it has been assumed that the vagotonic person inclines toward alkalosis and, therefore, shows a greater irrita-

TABLE 28—*The Results of Examinations of the Twenty Persons with the Highest Reactivity of the Muscles*

Individual Number	Muscle Reaction	Diagnosis	CO ₂ Combining Power	Potassium, Mg	K / Ca Ratio	Skin Resistance to Electric Current	Weight/Length Ratio	Pulse Rate	Vascular Reaction to Epinephrine	Systolic Blood Pressure
140	0.2	Glaucoma, tuberculosis, sensitized	55.6	29.7	2.61	0.45		70	Vagotonic	100
132	0.3	Sensitized, healed tuberculosis, eczema	40.3	15	1.12	0.31	234	56	Vagotonic	132
65*	0.4	Cardiovascular renal condition	53.1	16.4	1.67	0.80	221	63	Sympathetico-tonic	100
141	0.4	Glaucoma	64.6	28.2		0.20		84	Vagotonic	118
105*	0.6	Tuberculosis	54.1	15.3	1.47	0.44	196	71	Sympathetico-tonic	94
55*	0.6	Cardiovascular renal condition	56.6	24.9	3.10	0.38	170	84	Vagotonic	123
123*	0.6	Sensitized, cardiovascular renal condition	58.1	19.7	1.93	1	180	84	Sympathetico-tonic	122
139	0.8	Urticaria	50	18.4	1.90	0.20	176	104	Vagotonic	113
137	0.8	Glaucoma	51.9	18.2	2.24	1.90	166	78	Vagotonic	119
52*	1	Healed tuberculosis	52.9	20.9	2	0.13	213	75	Vagotonic	110
78*	1	Normal	62.7	18.8	2.23	0.62	203	74	Sympathetico-tonic	122
135	1	Nervous	54.5	19.6	1.65	0.09	183	88	Vagotonic	120
77*	1	Sensitized	60.6	15.6	1.44	1	187	82	Vagotonic	126
56*	1	Tuberculosis	56.6	28.6	2.52	0.32	247	80	Vagotonic	124
117	1	Syphilitic arthritis	52.4	17.5	1.80	0.25	195	78	Sympathetico-tonic	130
29*	1	Normal (bile in urine)	60.1	23.9	2.39	0.74	214	76	Sympathetico-tonic	134
7	1.2		55			0.30	202	68		118
25*	1.2	Tuberculosis	59.8	28.8	2.60	0.24	183	86	Sympathetico-tonic	140
14*	1.2	Syphilis, cardiovascular renal condition	55.3	18.3	1.55	0.33	200	92	Sympathetico-tonic	122
104*	1.2	Tuberculosis	57.2	22.9	3.09	0.08	235	84	Vagotonic	176
	0.82	Averages and totals	55.5	21	2.07	4.89	200	78.8	11 V, 8 S	122

* One of group of 100 "normal" men

bility. We have not been able to find any such correlation. Goebel and Hillenberg¹¹ were unable to confirm Hopman's conclusions. In the acidosis of pregnancy, Adersberg and Klafter¹² found a distinct increase in irritability.

10 Hopman, R. *Klin. Wchnschr.* 5:1553, 1926.

11 Goebel, F., and Hillenberg, S. *Arch. f. Kinderh.* 78:1, 1926.

12 Adersberg, D., and Klafter, E. *Klin. Wchnschr.* 6:2091, 1927.

When the tables of the results of the examinations of our extreme cases are examined, we find a distinct difference in the types of cases comprising them, as well as marked differences in the blood chemistry. Thus, it will be found that in the group with the greatest irritability are included a number of persons with roentgenologic evidence of active

TABLE 29—*The Results of Examinations of the Twenty Persons with the Lowest Reactivity of the Muscles*

Individual Number	Muscle Reaction	Diagnosis	CO ₂ Combining Power	Potassium, Mg	K / Ca Ratio	Skin Resistance to Electric Current	Weight/Length Ratio	Pulse Rate	Vascular Reaction to Epinephrine	Systolic Blood Pressure
91*	10	Normal	55.1	17.5	2.08	0.45	236	53	Vagotonic	134
76*	9.6	Cardiovascular renal condition	57.9	20.2	1.87	0.28	230	64	Sympatheticotonic	103
71*	9	Cardiovascular renal condition	57.9	17.5	2	0.36	195	88	Vagotonic	114
39*	8.5	Syphilis	55.7	18	1.91	0.29	254	82	Vagotonic	138
79*	7.7	Ulcer, cardiovascular renal condition	57	20	1.78	0.71	220	76	Sympatheticotonic	140
61*	7.4	Cardiovascular renal condition	53.1	17.9	2.35	0.28	208	64	Vagotonic	142
45*	7.4	Cardiovascular renal condition	54.3	16.6	1.48	0.28	317	84	Vagotonic	102
32*	7.4	Cardiovascular renal condition	54.1	26.1	2.73	0.18	190	74	Vagotonic	144
53*	6.7	Normal	53.9	22.8		0.35	231	80	Vagotonic	125
15*	6	Healed tuberculosis	57.6	18.8	1.55	0.19	210	60	Sympatheticotonic	128
17*	6	Normal	59.1	18.2	1.43	0.22	216	66	Vagotonic	130
82*	5.7	Cardiovascular renal condition	58.8	17.2	1.50	0.20	208	62	Sympatheticotonic	170
98*	5.5	Cardiovascular renal condition	62.7	17	1.93	0.20	212	64	Vagotonic	136
75*	5.4	Cardiovascular renal condition	61.6	19.2	1.78	0.13	243	77	Vagotonic	146
47*	5	Healed tuberculosis	56.4	26.2	2.51	0.13	260	70	Vagotonic	136
20*	5	Tuberculosis	62.7	17.4	1.53	0.25	226	80	Vagotonic	130
62*	5	Cardiovascular renal condition	56.8	15.2	1.30	0.15	221	64	Vagotonic	140
64*	5	Normal, nervous	55	16.6	1.84	0.22	208	64	Vagotonic	112
68*	4.4	Healed tuberculosis	51.1	17.1	1.94	0.53	217	89	Sympatheticotonic	131
63*	5	Cardiovascular renal condition	62.4	20.9	1.83	0.65	190	60	Vagotonic	116
6.58 Averages and totals			57.1	19.1	1.85	0.30	224	71	15 V, 5 S,	134

* One of group of 100 "normal" men

tuberculosis, as well as sensitized persons. In the group with the lower irritability are many persons with cardiovascular renal lesions and increased blood pressure (tables 28 and 29).

The persons with the greatest irritability have more serum potassium, higher K/Ca ratios, greater skin resistance and higher pulse rates and are somewhat lighter in weight.

MUSCLE REACTION

10
8.
8
7
6
5
4.
3
2
1.

Normal Range

3.2

Normals
Healed TB w Wassermann
Roentgen active TB

Low bl pr Urine +
Normal bl pr Urine +
Increased bl pr Urine +
Art se or my Capillaries

Chart 10—The muscle reactivity of normal persons and patients with various clinical conditions

REACTION OF PULSE PRESSURE TO EPINEPHRINE

In a previously published paper,⁸ we made an analysis of the present material when the results of the reaction to epinephrine (subcutaneous injection of 0.5 cc. of epinephrine hydrochloride, 1 to 1,000) are estimated wholly on the increase or decrease in the systolic blood pressure. In that paper, we pointed out that when we selected a group of ten of the most markedly sympathetotonic persons and compared them with the ten most markedly vagotonic persons, the sympathetotonic ones had higher calcium levels, but lower K/Ca ratios, shorter Kromayer lamp erythema times, lower blood pressures and CO₂ combining powers, lower weight/length ratios and somewhat greater wheals due to thyroxin, and greater flares due to epinephrine and thyroxin.

When we examine tables 30 and 31 containing the results of the examinations of the twenty persons showing the greatest and the least reactivity to epinephrine based on the percentage of increase or decrease in pulse pressure for one hour following the injection, we, of course, deal with a somewhat different group of persons. In both instances, we deal with persons who give either a primary sympathetotonic or a vagotonic systolic reaction, but inclusion in this group will depend rather on the sustained character of these reactions.

The blister times for the sympathetotonic group so constituted are longer, the levels of calcium are somewhat higher, the blood pressures are lower, the levels of the blood sugar are higher and the persons are not so heavy. The flares due to epinephrine and the wheals due to thyroxin are larger.

In our former study of this material, we found that the low K/Ca ratio which Kylin assumed for the sympathetotonic group was apparent only for a relatively small, selected group, while many of the persons with a distinctly sympathetotonic type of reaction had high ratios. It should be noted that with the present classification, the difference in the ratio which Kylin postulates does not appear. In general, however, the sympathetotonic group has a higher level of calcium.

Chart 11 reveals the wide range of our normal persons, as well as of the persons with cardiovascular renal conditions. In the latter group, however, certain differences do appear. Those with low blood pressures and positive evidence of changes in the urine appear at the vagotonic end. Patients with exophthalmic goiter, as might be anticipated, are found toward the sympathetotonic end.

TABLE 30—The Results of Examinations of the Twenty Persons with the Greatest Increases of Pulse Pressure Following the Subcutaneous Injection of Epinephrine Hydrochloride

Individual Number	Reaction to Epinephrine Pulse Pressure Increase, %	Diagnosis	Blister Time, Hr	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K / Ca Ratio	Globulin, Mg	Blood Pressure, Systolic	Blood Pressure, Diastolic	Sugar, Mg	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
8*	66	Normal	10	64	6.4	10.5	21	2	45	120	96	73	197	Sympathetotonic +	20.4	9.8	11.2	0
51*	66	Cirrhosis, cardiovascular renal condition	6	60	10		22		33	108	88	80	256	Sympathetotonic —	21.2	13.4	12	0
2*	64	Epilepsy	7	69	9.8	12.9	26.1	2		100	68	74		Sympathetotonic +	17	11.2	15	0
167	62	Glaucoma	15	56	3.7	12	22.7	1.9	27	137	92	81	185	Sympathetotonic +	18.4	9.7	15.4	12
127*	60	Cardiovascular renal condition	13	50	3.8	12.2	16.2	1.33	33	106	76	81	180	Sympathetotonic +	22.4	16	18	16
172	57	Raynaud's disease	12	72	0	13	21.3	1.64		108	78	76	166	Sympathetotonic +	16.8	12.6	6.6	0
24*	50	Healed tuberculosis	6	70	11.6	11.7	24.8	2.12	60	116	58	81	219	Sympathetotonic +	14.4	11.5	15	0
144	50	Cardiovascular renal condition, pellagra	15	35	2.2	9.8	17.9	1.79	2	100	66	90	174	Sympathetotonic +	20.4	10.2	15.2	7.6
92*	46	Nervous	9	82	9	8.4	19.5	2.32	26	110	60	67	210	Sympathetotonic +	18	13.6	16	0
145	43	Glaucoma	15	67	4.4	10.1	15.7	1.55	55	136	80	70	166	Sympathetotonic —	16	8.8	12	5.4
87*	40	Normal	6	56	9.3	8.4	19.5	2.32	30	104	62	94	200	Sympathetotonic +	20	9.2	10.2	0
66*	37	Cardiovascular renal condition	6	78	13	11	20	1.8		128	65	67	237	Sympathetotonic +	20	8	13.2	9.6
133	36	Scleroderma				13.2	17.5	1.32	90	92	68	77	202	Sympathetotonic +	20	21.2	9	15.2
1	35	Neurosis	8	68	8.5	12.1	24.9	2	38	132	71	113		Sympathetotonic +	18.6	8.7	17	0
23*	35	Tuberculosis	6	57	9.5	11.1	28.8	2.6	19	140	80	67	183	Sympathetotonic —	22.8	11	9.2	0
142	33	Tumor of the brain	7	54	7.7	9.4	18.3	1.95	19	108	78	97	200	Sympathetotonic —	17.2	11.8	12.2	11.2
35*	33	Normal	8	54	6.7	8.7	25.2	2.9	33	108	78	79	203	Sympathetotonic —	19.2	9.6	12	7
53*	32	Normal	8	62	7.7		22.8		25	125	73	77	231	Sympathetotonic +	21.2	7	11	0
68*	31	Healed tuberculosis	7	78	11	8.8	17.1	1.94	30	131	76	68	217	Sympathetotonic +	20	10.8	13	4.6
83*	31	Cardiovascular renal condition	6	58	9.6	11.4	17.2	1.5	33	170	98	58	208	Sympathetotonic +	20	10.8	13	4.6
20	41	Averages	8.9	62	7.8	10.8	20.9	1.93	35	113	73	78	195					

* One of group of 100 "normal" men

TABLE 31—The Results of Examinations of the Twenty Persons with the Lowest Increases of Pulse Pressure Following the Subcutaneous Injection of Epinephrine Hydrochloride

Individual Number	Reaction to Epinephrine Pulse Pressure Increase, %	Diagnosis	Blister Time, Hr	Permeability of Capillaries	Inflammatory Index	Calcium, Mg	Potassium, Mg	K / Ca Ratio	Globulin, Mg	Blood Pressure, Systolic	Blood Pressure, Diastolic	Sugar, Mg	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
116	—17	Urticaria	3.5	60	17	10	19.4	1.94	40	125	50	87	195	Vagotonic	20.4	7.4	9	0
121	—13	Arthritis deformans	6	60	11.5	8.9	20.2	2.27	30	148	80	74	294	Vagotonic	26	5.6	8	0
80*	—12	Nervous	15	58	3.8	12.6	15.9	1.26	10	118	60	64	176	Vagotonic	18.8	11	15.4	12.4
129*	—10	Tuberculosis	15	52	3.5	11.5	19	1.65	42	116	66	83	219	Vagotonic	18.1	7	12.2	0
88*	—10	Tuberculosis	7.25	58	8.1	9.1	13.1	1.4	33	128	76	79	205	Vagotonic	18.4	11	12.4	12
135	—10	Nervous	6	84	14	11.9	19.6	1.65	45	120	60	75	183	Vagotonic	12.4	3.2	20	0
75*	—9	Cardiovascular renal condition	9	60	6.6	10.8	19.2	1.78	38	146	80	75	243	Vagotonic	20.4	10.8	10	0
118	—8	Arthritis	10	87	8.7	12.2	17.2	1.4	35	120	60	80	154	Vagotonic	16.8	7.1	12	8.6
67*	—8	Dwarf	6	71	11.8	8.8	17.6	2	33	123	80	56	195	Vagotonic	17.2	9	13.6	0
37*	—8	Normal	9	56	6.2	10	22.6	2.26	42	116	70	75	254	Vagotonic	20.4	21.6	10	0
70*	—8	Arthritis	10.5	74	7	11.1	16.6	1.45	34	148	50	67	214	Vagotonic	18	11	10	0
47*	—5	Healed tuberculosis	5	62	12.8	10.1	26.2	2.51	40	136	64	72	266	Vagotonic	21.6	5	9	0
132	—5	Angioneurotic edema	4	73	18	9.8	20.1	2.05	20	120	74	63	243	Vagotonic	23	7.5	9	8
106*	—5	Cardiovascular renal condition	6	71	12	11.2	19	1.69	37	120	68	65	243	Vagotonic	19.6	7	11.2	0
110*	—4	Healed tuberculosis	7.5	54	7.2	12.1	16.3	1.34	28	110	62	61	190	Vagotonic	20.8	1.2	12	9.4
123	—3	Carcinoma of thyroid, hyperthyroidism	9.25	74	8	9.2	20	2.17	32	165	110	81	263	Vagotonic	20	6.8	10	12.2
45*	—3	Cardiovascular renal condition	6	54	9	11.2	16.6	1.48	40	162	111	77	317	Vagotonic	20.1	9.8	16.1	12
122*	—3	Normal	4	68	17	10.6	19.2	1.81	35	102	50	50	189	Vagotonic	20	7.8	12	9
103*	—1	Cardiovascular renal condition	6	52	8.6	9.2	17.3	1.88	40	126	70	57	270	Vagotonic	22.1	9	12.2	0
107*	—1	Cardiovascular renal condition	9	58	6.4	8	18.4	2.3	40	131	72	60	265	Vagotonic	20.8	5.8	13.1	6.2
—7	Averages		7.7	64	9.6	10.4	18.6	1.8	41	128	71	71	242		19.8	8.3	11.6	4.4

* One of group of 100 "normal" men

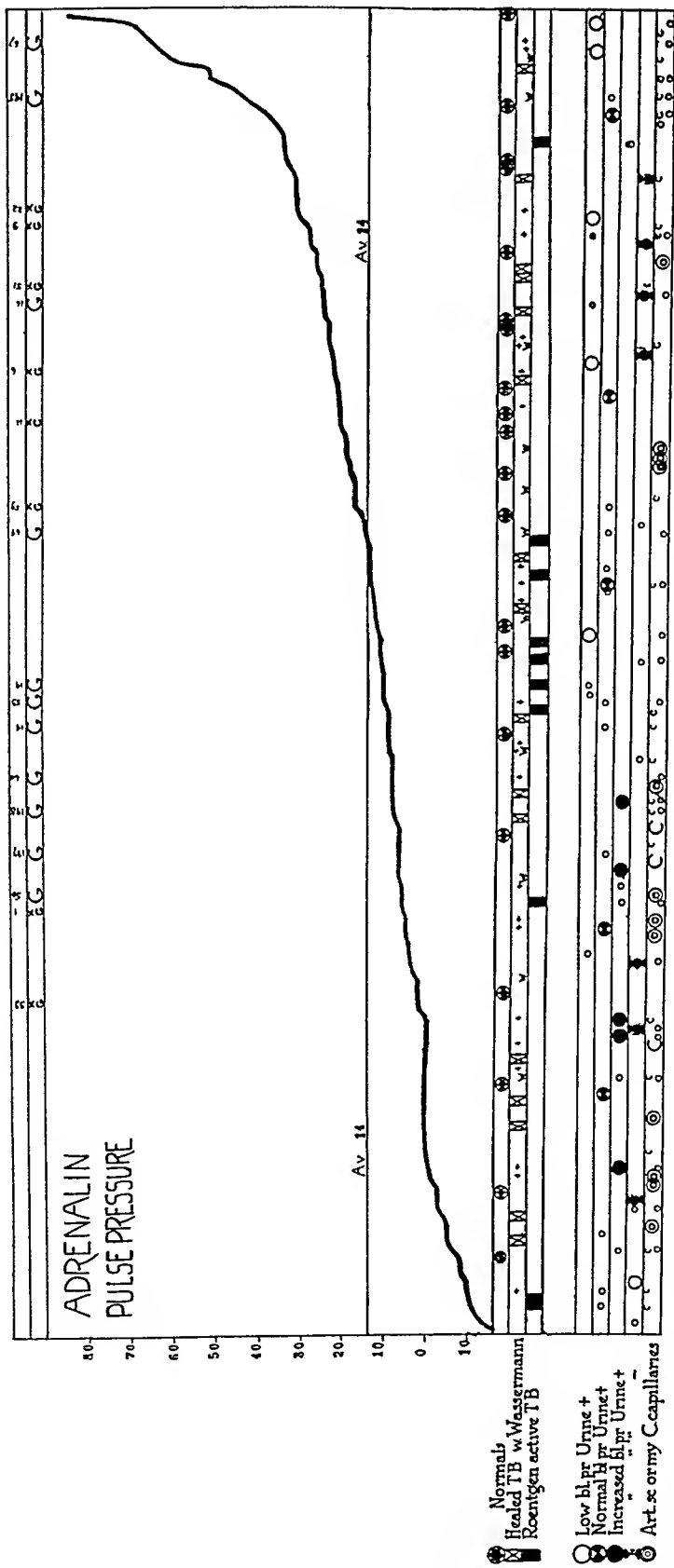


Chart 11—The pulse pressure increase following the subcutaneous injection of epinephrine hydrochloride in normal persons and patients with various clinical conditions

CO₂ COMBINING POWER

The average CO₂ combining power of the serum of the 100 "normal" men was 57.7. The range for the strictly normal persons was from 52 to 65. Chart 12 indicates that all the persons in the healed tuberculous group are uniformly distributed over the normal range, the per-

TABLE 32—*The Results of Examinations of the Ten Persons with the Lowest CO₂ Combining Powers*

Individual Number	CO ₂ Combining Power	Diagnosis	Potassium, Mg	Calcium, Mg	Ice Reaction Time, Seconds	Weight/Length Ratio	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
132	40.3	Eczema	15	13.4	10	234	18.4	9.4	13.4	5
167	47.9	Glaucoma	22.7	12	5	158	17	14.2	15	0
171	48.7	Urticaria	17.9	12.6	20	161	17.5	10.5	18	0
161	49.4	Glaucoma	18	9.2	12	171	14	13	13	0
106	49.5	Cardiovascular renal condition	19	11.2	30	243	19.6	7	11.2	0
139	50	Urticaria	18.4	9.7	8	176	16	11	14	12.5
68	51	Healed tuberculosis	17.1	8.8	10	217	19.2	9.6	12	7
109	51.4	Neurosis	16.1	10.8	25	140	18	9	12	9.4
115	51.8	Cardiovascular renal condition	15.2	7.8	10	215	17.2	6	14.2	8
137	51.9	Glaucoma	18.2	8.1	30	166	15.4	10.5	13	0
49.2	Averages		17.7	10.36	16	188	17.2	10	13.5	4.19

TABLE 33—*The Results of Examinations of the Ten Persons with the Highest CO₂ Combining Powers*

Individual Number	CO ₂ Combining Power	Diagnosis	Potassium, Mg	Calcium, Mg	Ice Reaction Time, Seconds	Weight/Length Ratio	Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
153	73.2	Glaucoma	18.7	9	30	223	22	6.5	18	0
150	72.7	Glaucoma	21.3	12	7	238	17	14	16	0
146	71	Myasthenia	14.4	9.2	30	192	18	12	19	0
148	69.6	Glaucoma	24.3	9.7	10	182	18	12	17	0
28	66	Healed tuberculosis	24.1	11	25	200	20	12.2	7.4	0
149	65.4	Nervous	17	10.1	15	209	20	9.7	19	0
14	65	Cardiovascular renal condition	19.6	11.2	40	198	24.4	6.2	15	5
50	65	Normal	27.4	18.4	15	237	24.8	10.6	10.4	10
4	64.3	Normal	21.2	11.8	40	237	22.8	10.6	10.2	0
105	64.4	Healed tuberculosis	17.1	9	15	194	19.6	5.6	12	10.4
67.6	Averages		20.5	10.4	22.7	211	20.6	9.94	14.4	2.5

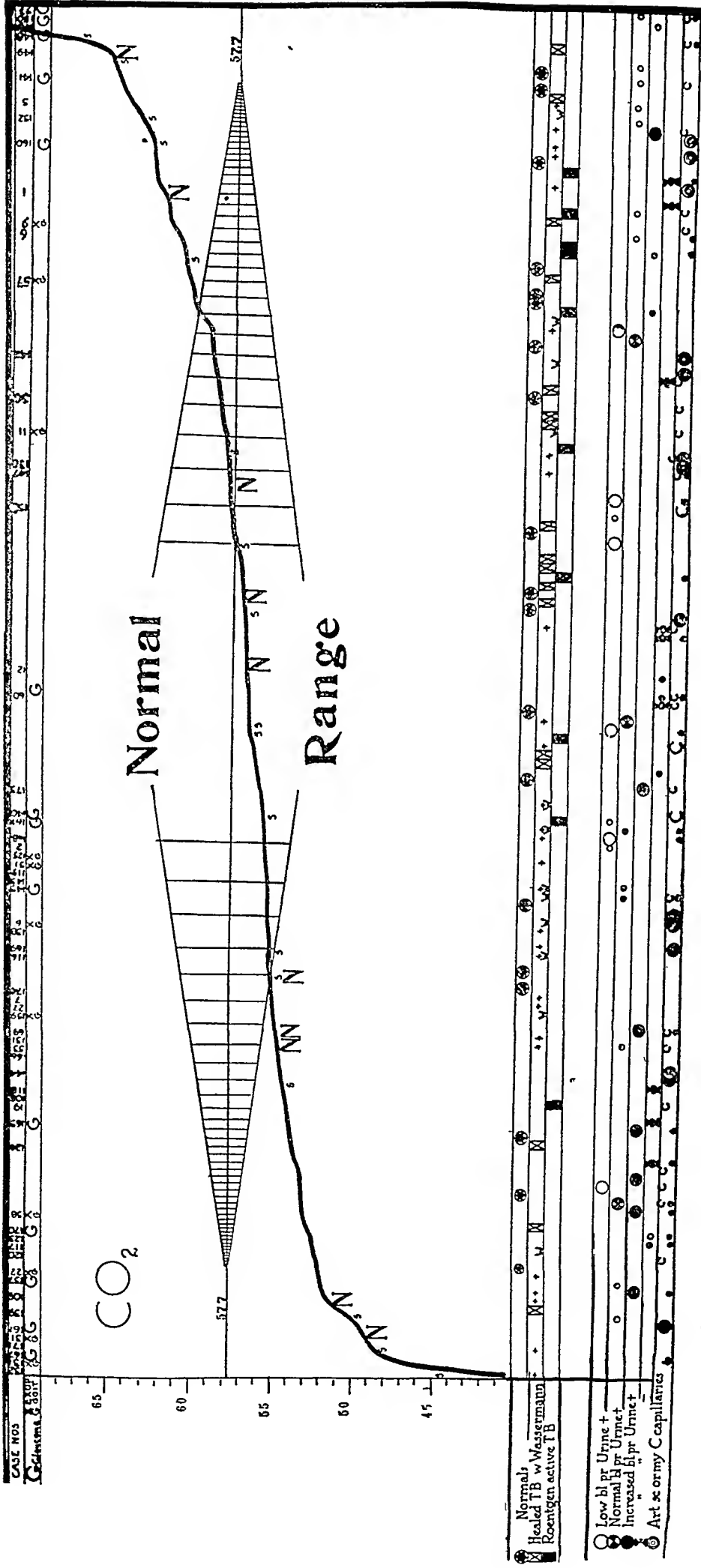


Chart 12—The CO₂ combining power of the serum of normal persons and patients with various clinical conditions

sons with active tuberculosis tend to appear at the upper end of the curve. There appears to be nothing characteristic in the distribution of the various groups with cardiovascular renal conditions, unless it is the fact that those with increased blood pressure and urinary changes appear at the low end of the scale.

Sensitized and nervous persons are found over the entire range. More of the patients with exophthalmic goiter and glaucoma are found on the side below the average.

We have tabulated the results of some examinations of the ten persons with the lowest and of the ten with the highest CO_2 combining powers in tables 32 and 33.

It will be observed that the person (no. 132) with the lowest CO_2 combining power is the one with eczema who previously was outstanding because of a low K/Ca ratio. Two persons with urticaria also appear in this group. The types of persons in the group with high CO_2 combining power are of no particular interest. The chief divergencies of the group with low CO_2 combining power appear to be their shorter ice reaction times and smaller wheals due to epinephrine. The potassium values, too, are perceptibly diminished.

ICE REACTION TIME

The rapidity with which an erythema appears following the local application of ice to the skin affords some insight concerning the activity of the peripheral vasomotor apparatus. In these observations, we have uniformly used the chest wall. In the table of correlation (part I, table 1), we have shown the following apparent correlations of the ice reaction time: delay of the reaction (1) with increasing level of calcium, (2) with increasing metabolic rate, (3) with increasing CO_2 combining power (except with exophthalmic goiter), (4) with increasing age, (5) with decrease of the flare due to thyroxin and of the wheal to caffeine, and acceleration with increasing weight/length ratio.

Tables 34 and 35, based, respectively, on the extremely rapid reaction and the delayed reaction, confirm the relation to the level of calcium, to the metabolic rate, to the weight/length ratio, to age and to the flare due to thyroxin. In addition, it appears that with delayed ice reaction, the resistance of the skin to electric current is greater. The proportion of sympathetotonic persons is slightly larger in the group with short ice reaction time.

When we examine chart 13, we find the strictly normal group scattered over the entire curve, but it may be observed that almost half of the group are clustered in one region (the range from 18 to

TABLE 34—*The Results of Examinations of the Twenty Persons with the Most Rapid Reactions to Local Application of Ice to the Chest*

Individual Number	Ice Reaction Time, Seconds	Diagnosis	Calcium, Mg	Inflammatory Index	Protein, Mg	Skin Resistance to Electric Current	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Thyroxin, Flare, Mm	Caffein, Wheal, Mm	Weight/Length Ratio	Age
67*	4	Dwarf	88	11.8	6.08	0.19	32	Vagotonic	0	33.4	195	47
123*	5	Normal	106	17	8.06	0.37	-7.3	Vagotonic	9	21.2	189	33
100*	5	Healed tuberculosis	9	9	7.85	0.11	-1.6	Vagotonic	29.2	27	241	45
163	5	Glaucoma	10	5.4	8.28	0.18	0.5		0	15	250	52
168	5	Orthostatic albuminuria	9.4	12	7.41	0.16	-9	Vagotonic	0	23	215	28
167	5	Glaucoma	12	3.7	8.71	0.85	-13	Sympatheticotonic	0		158	77
142	5	Tumor of the brain	9.4	7.7	7.69	0.17	+5	Sympatheticotonic	0	30	200	53
103*	5	Cardiovascular renal condition	9.2	8.6	7.73	0.39	+2	Vagotonic	0	18.2	270	59
61*	7	Cardiovascular renal condition	7.6	11.6	7.41	0.28	+1	Vagotonic	0	20.2	208	51
41*	7	Normal	9.8	9.1	8.49	0.26	+15	Vagotonic	0	5.8	216	40
10*	7	Healed tuberculosis	10.1	13	8.70	0.42	-12.4	Vagotonic	7.2	12.2	230	40
64*	7	Normal	9	10	7.41	0.22	+23	Sympatheticotonic	11.6	16.2	208	31
43*	7	Normal	9.2	9.7	7.63	0.27	-4.4	Sympatheticotonic	0	11	231	45
150	7	Glaucoma	12	3.8	7.85	0.22	+39	Vagotonic	0	22	238	67
139	8	Urticaria	9.7	11	7.10	0.20	+5	Vagotonic	12.5	14	176	29
78*	10	Normal	8.4	12	8.49	0.62	-6.2	Sympatheticotonic	6.2	20	203	33
18*	10	Healed tuberculosis	14.5	8.7	8.30	1	+4.2	Vagotonic			200	31
95*	10	Healed tuberculosis	7.8	9.8	8.5	0.39	+26	Sympatheticotonic	6.2	26.2	220	54
59*	10	Normal	9.6	8.6	7.85	0.16	-6.5	Vagotonic	8	23.4	252	37
68*	10	Healed tuberculosis	8.8	11	8.66	0.53	+25.8	Sympatheticotonic	7	22.4	217	35
69		Averages and totals	9.74	9.67	7.95	0.349	+5.9	7 S, 12 V	5.1	20	215	44.3

* One of group of 100 "normal" men

TABLE 35—*The Results of Examinations of the Twenty Persons with the Least Rapid Reactions to the Application of Ice to the Chest*

Individual Number	Ice Reaction Time, Seconds	Diagnosis	Calcium, Mg	Inflammatory Index	Protein, Mg	Skin Resistance to Electric Current	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Thyroxin, Flare, Mm	Caffein, Wheal, Mm	Weight/Length Ratio	Age
91*	45	Cardiovascular renal condition		8	7.85	0.30	-1.7	Vagotonic	9.4	22.2	208	66
70*	45	Arthritis, cardiovascular renal condition	11.4	7	8.65	0.39	+23	Vagotonic	0	24.6	264	65
81*	45	Pruritis, cardiovascular renal condition	8.4	10	8.49	0.10	+34.8	Vagotonic	0	16.4	209	69
136	45	Arteriosclerosis, pellagra	10	5	9.28	0.39	+20	Sympatheticotonic	0	16	180	44
172	45	Raynaud's disease	13	6	8.16	0.08	+18	Sympatheticotonic	16	20	166	30
14*	40	Cardiovascular renal condition	11.2	10.5	8.06	0.20	+2.7	Vagotonic	5	9.8	198	36
40*	40	Changes in capillaries	10.8	6.6	8.70	0.39	+22	Vagotonic	0	5.8	201	40
40*	40	Changes in capillaries	10.2	6.6	8.70	0.39	+22	Vagotonic	0	5.8	201	40
96*	40	Cardiovascular renal condition	8.2	7	7.26	0.11	+31	Vagotonic	0	28.4	213	70
102*	40	Tuberculosis	10.6	5.8	7.95	0.20	+22	Vagotonic	0	18.2	170	65
140	40	Tuberculosis glaucoma	11.4	4.05	6.77	0.45		Vagotonic	0	30		45
15*	38	Healed tuberculosis	12.1	7.5	7.95	0.19	-4.5	Sympatheticotonic	12	12.4	210	60
26*	35	Syphilis	10.2	11	8.28	0.28	+9.6	Vagotonic	6.4	11.6	210	30
48*	35	Syphilis	9.6	9.7	8.59	0.10	8.3	Sympatheticotonic	0	7	222	46
77*	35	Sensitized	10.8	10	6.98	1	7.9	Vagotonic	15.4	17	187	39
73*	35	Syphilis	11.2	7.6	8.5	2	16.3	Vagotonic	0	20	191	48
158	35	Hodgkin's disease	9.3	4	8.28	0.29	37	Sympatheticotonic	0	22	173	49
42*	32	Cardiovascular renal condition	11.4	6.5	7.63	0.15	6.8	Vagotonic	4.6	5.8	211	33
80*	30	Nervous	8	15.1	8.28	1.6	13	Vagotonic	9.2	16.2	212	30
106*	30	Cardiovascular renal condition	11.2	12	8.06	0.63	-6.6	Vagotonic	0	25.6	243	60
137	30	Glaucoma	8.1	4	8.49	1.9	3.6	Vagotonic	0	18	166	61
35		Averages and totals	10.3	7.86	8.11	0.537	+12	15 V, 5 S	3.9	19.96	204	49.3

* One of group of 100 "normal" men

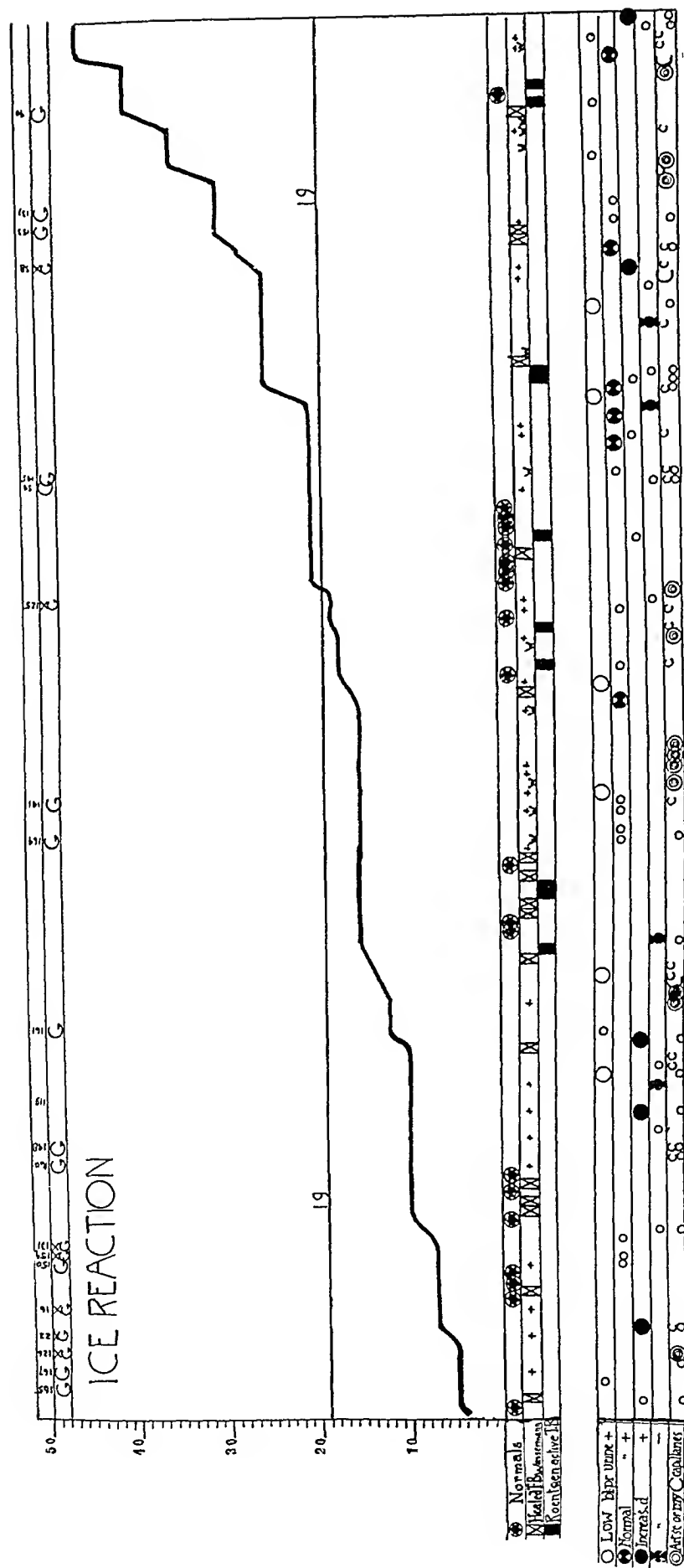


Chart 13 —The ice reaction time of normal persons and patients with various clinical conditions

20 minutes) This group is composed of those persons who were noted for relatively low capillary permeability, and some of them show a sluggish capillary circulation

The persons with roentgenologic evidence of active tuberculosis appear toward the side of the curve representing delay, and it seems that more of the group with cardiovascular renal conditions are found here The advanced ages of the members of both these groups must be taken into consideration

WEIGHT/LENGTH RATIOS

The average weight/length ratio (weight in pounds, length in inches) for our group of 100 "normal" men is 217 (chart 14) When we select the twenty persons with the highest ratios, it is evident that the group includes most of the persons in whose cases a roentgenologic diagnosis of myocarditis was made The majority give a vagotonic reaction to epinephrine, and their K/Ca ratios average 2.06

In part I, table 1, the correlations with the weight/length ratio indicate that as the ratio increases the capillary permeability diminishes, the K/Ca ratio increases, the sugar increases, the basal metabolic rate decreases, as also does the skin resistance, the pulse pressure on subcutaneous injection of epinephrine hydrochloride and the CO₂ combining power increase, and the wheal due to epinephrine and the flare due to morphine increase

In tables 36 and 37, the averages for the sugar and the basal metabolic rate show little difference between the two extreme groups, but there are more persons with high skin resistance in the group with the highest ratios The wheals due to epinephrine are larger here, as are the flares due to morphine, while the wheals due to thyroxin are smaller

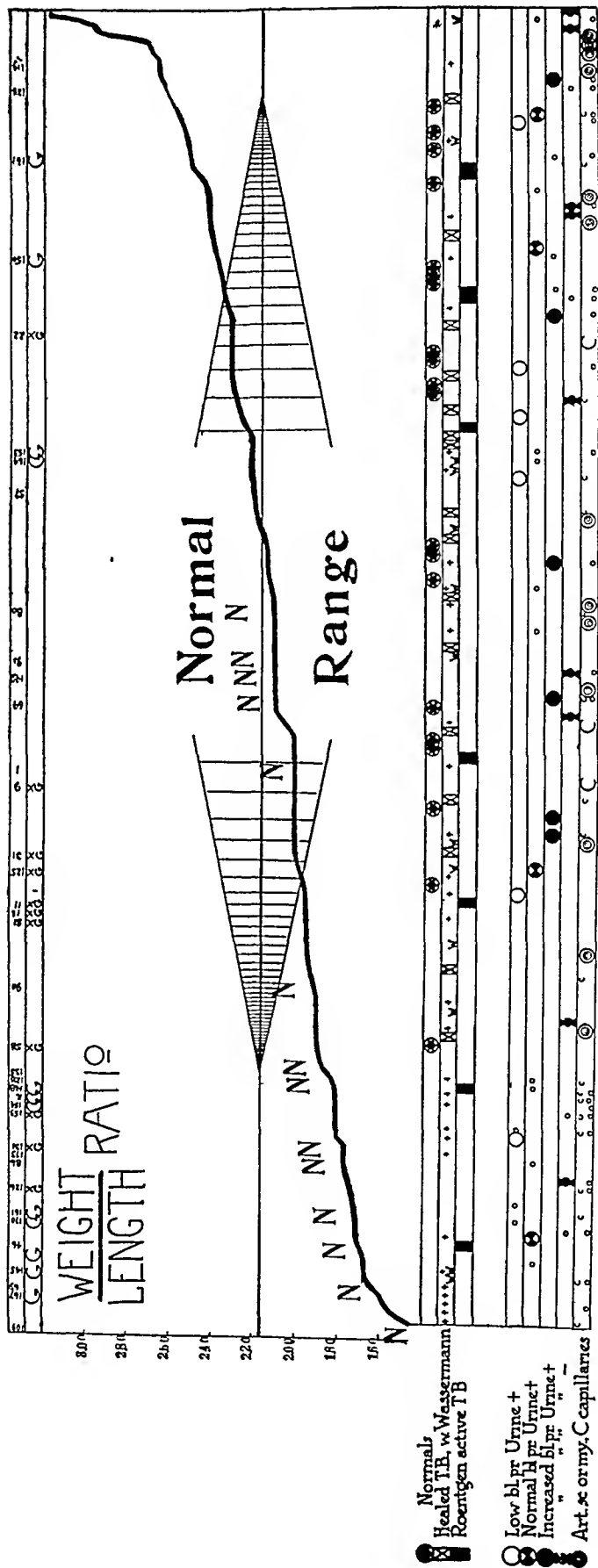


Chart 14 —The weight length ratio of normal persons and of patients with various clinical conditions

TABLE 36—The Results of Examinations of the Twenty Persons with the Lowest Weight/Length Ratios

Individual Number	Weight/Length Ratio	Diagnosis	K / Ca Ratio	Sugar, Mgs	Basal Metabolic Rate	Skin Resistance to Electric Current	CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wbeat, Mm	Morphine, Wbeat, Mm	Morphine, Wbeat, Mm	Thyroxine, Wbeat, Mm	Thyroxine, Wbeat, Mm	
174	143	Raynaud's disease	2	90	4	0.47	55	Vagotonic	0	18	9	9	7.2	12	9.4
109	140	Neurosis	1.5	67	—	0.54	51.4	Vagotonic	3	18	9	12	7.4	13	0
147	142	Postencephalitis	2	79	—6	0.54	57.9	Sympatheticotonic	8	18	11.6	12	7.4	13	0
118	151	Arthritis	1.4	80	—11	1.9	54.2	Vagotonic	—8	16.8	7.4	10	6.8	12	8.6
167	138	Glaucoma	1.9	81	—13	0.85	47.9	Sympatheticotonic	+6.2	17	14.2	12	9	15	0
69	160	Ulcer, nervous	1.66	70	+4	1.9	54.8	Sympatheticotonic	0	21.2	10	12.2	22	14.4	10.2
171	161	Urticaria	1.42	72	8	0.08	48.7	Sympatheticotonic	12	17.5	10.5	12.5	0	18	0
145	166	Wassermann reaction +, glaucoma	1.55	70	19	0.35	55.4	Sympatheticotonic	43	18	13.6	16	0	16	0
172	165	Raynaud's disease	1.64	76	15	0.08	51.9	Sympatheticotonic	57	22.4	16	15.5	8.5	18	16
137	166	Glaucoma	2.24	73	3.6	1.9	51.9	Vagotonic	7	15.4	10.5	12.5	10	13	0
46*	168	Inanition	1.24	61	13	1.7	56.2	Sympatheticotonic	15	21.2	13.2	15	16.2	12.2	11
102*	170	Tuberculosis	1.63	62	22	0.20	60.9	Vagotonic	11	23.2	7.4	10.8	15	12.2	0
55*	170	Cardiovascular renal condition (urine)	3.1	73	6.2	0.33	56.6	Vagotonic	5	17.6	8.2	10.2	19.6	11.2	0
170	170	Glaucoma	2.2	320	33	0.07	52.5	Sympatheticotonic	25	14	13	5.5	10.7	13	0
161	171	Glaucoma	1.96	86	16	1.4	49.4	Sympatheticotonic	25	21.2	7.2	9.6	8.2	12	0
120	172	Purpura	1.99	71	—5	0.29	52.2	Sympatheticotonic	10	19.2	11.3	13	0	28	0
138	173	Hodgkin's disease	2	83	+37	0.5	57.8	Sympatheticotonic	50	14.4	11.5	12.6	12.5	15	0
144	174	Pellagra	1.70	90	—3.7	0.5	54.4	Sympatheticotonic	0	20	8.8	8.2	16	7.2	0
30*	175	Arteriosclerosis, cardiovascular renal condition	2.33	76	—5.9	1.05	62.5	Vagotonic	—12	18	14	11.8	19.6	15.4	12.4
86*	176	Nervous	1.26	94	+6.4	0.36	55	Vagotonic	15	18.5	10.9	11.6	9.9	14.3	3.7
163	Averages and totals		1.89	76	7.6	0.77	53.9	10 S, 8 V							

* One of group of 100 "normal" men

TABLE 37—The Results of Examinations of the Twenty Persons with the Highest Weight/Length Ratios

Individual Number	Weight/Length Ratio	Diagnosis	K / Ca Ratio	Sugar, Mgr	Basal Metabolic Rate	Skin Resistance to Electric Current	Vascular Reaction to Adrenaline	Epinephrine, % Increase in Pulse Pressure	Epinephrine, Wbeat, Mm	Epinephrine, Flare, Mm	Morphine, Wbeat, Mm	Morphine, Flare, Mm	Thyroxin, Wbeat, Mm	Thyroxin, Flare, Mm
15*	317	Increased blood pressure (above 140)	1.18	77	20	0.28	Vagotonic	-3	20.1	9.8	11.2	21.1	16.1	12
6	300	Arteriosclerosis, myocarditis	1.80	70	29	0.30	Vagotonic	0						
121	294	Arthritis deformans	2.27	71	11	0.28	Vagotonic	-13	26	5.6	10.2	8.8	8	0
103*	270	Arteriosclerosis, myocarditis	1.88	37	2	0.39	Vagotonic	-1	22.4	9	12.2	18.2	12.2	0
138	270	Myocarditis, Frohlich's syndrome	1.88	83	8	0.07	Vagotonic	-0	23	9.5	12.5	8.7	17	6.5
98*	267	Myocarditis, hay fever	3.22	70	0	0.25	Sympatheticotonic	+19	20.1	8.6	12.4	15	10	0
119	266	Adenoma of the thyroid	2.1	77	34	0.08	Sympatheticotonic	+13	24	5	12	11.2	12	7
107*	265	Arteriosclerosis, myocarditis	2.3	60	-6.5	0.33	Vagotonic	-1	20.8	5.8	8.6	11.2	13.4	6.2
70*	264	Arteriosclerosis, arthritis deformans	1.45	67	23	0.39	Vagotonic	-6	18	11	9.8	18.2	10	0
123	263	Arteriosclerosis, eucromia of the thyroid	2.17	81	18		Vagotonic	-3	20	6.8	11.2	10.2	10	12.2
17*	260	Healed tuberculosis	2.51	72	34	0.13	Vagotonic	-5	21.6	5.2	11.2	10.8	9	0
83*	258	Normal	2.31	68	-7	0.16	Vagotonic	+9.6	17.2	9.2	9.2	20.8	13.1	11
60*	257	Arteriosclerosis, myocarditis	1.82	67	13	0.37	Sympatheticotonic	+37	20	9.2	13.6	16.6	10.2	0
54*	256	Myocarditis		80	-3.1	0.26	Sympatheticotonic	+66	21.2	10.1	11	18	12	0
37*	254	Normal	2.26	75	-21.1	0.34	Vagotonic	-8	20.1	21.6	18	15.2	10	0
39*	251	Syphilis	1.91	79	13.1	0.29	Vagotonic	+17	18	9.8	13.8	9.8	7.6	5
59*	252	Normal	1.88	85	-6.5	0.16	Vagotonic	+2	22	7.2	9.2	21.4	15.6	8
165	250	Arteriosclerosis, glaucoma	1.79	80	0.5	0.18			16.8	13	10	11.5	12.5	0
129*	249	Tuberculosis	1.65	83	+28	0.22	Vagotonic	-10	18.4	7	10.6	9.6	12.2	0
56*	247	Tuberculosis	2.52	65	+17.9	0.32	Vagotonic	+11	17.2	5.8	10.8	22.1	13.1	7
265.6	Averages and totals		2.06	73.4	9.3	0.25	15 V, 4 S	6.2	19.8	8.9	11.7	15.4	11.8	3.9

CHOLESTEROL

The determinations of cholesterol were made on 109 members of the groups of "normal" persons and patients, the average amount for the persons of the "normal" group being 207 mg

In chart 15 we illustrate this material. Of the actually normal persons, we have only eight for consideration, and have placed the normal range at from approximately 160 to 245. Of this group, patient 92 falls far outside this range, having a cholesterol level of over 300.

Furthermore, it appears that the group with the higher levels of cholesterol includes more persons with histogenologic evidence of

TABLE 38—*The Results of Examinations of the Twenty Persons with the Highest Values of Cholesterol*

Individual Number	Cholesterol, Mg	Diagnosis	Reaction to Epinephrine
95	318	Healed tuberculosis	Sympatheticotonic
148	317	Vitiligo, glaucoma	Vagotonic
94	303	Normal	Vagotonic
111	290	Cardiovascular renal condition	Sympatheticotonic
14	278	Cardiovascular renal condition	Vagotonic
75	278	Cardiovascular renal condition	Vagotonic
109	269	Neurosis	Vagotonic
141	267	Glaucoma	Vagotonic
173	267	Tumor of the cord	Sympatheticotonic
61	264	Cardiovascular renal condition	Vagotonic
62	256	Cardiovascular renal condition	Vagotonic
167	256	Glaucoma	Sympatheticotonic
107	256	Cardiovascular renal condition	Vagotonic
132	256	Eczema	Vagotonic
71	256	Cardiovascular renal condition	Vagotonic
136	256	Pellagra	Sympatheticotonic
115	247	Cardiovascular renal condition	Vagotonic
127	247	Cardiovascular renal condition	Sympatheticotonic
150	247	Glaucoma	Vagotonic
73	247	Syphilis	Vagotonic
Average	268	Total	6 S, 14 V

healed parenchymal tuberculosis. In connection with the group with cardiovascular renal lesions, the outstanding fact seems to be that there are more persons with arteriosclerosis in the group with the high levels of cholesterol. This seems true for the 100 "normal" men, as well as for all the persons examined.

In tables 38 and 39, we have tabulated the results of some examinations of the twenty persons with the highest and lowest cholesterol values (excluding those with exophthalmic goiter). There are obviously more persons with arteriosclerotic changes and increased blood pressure on the side of the high values of cholesterol than on the side of the low values. It appears, too, that this group includes more persons with a distinctly vagotonic reaction to epinephrine.

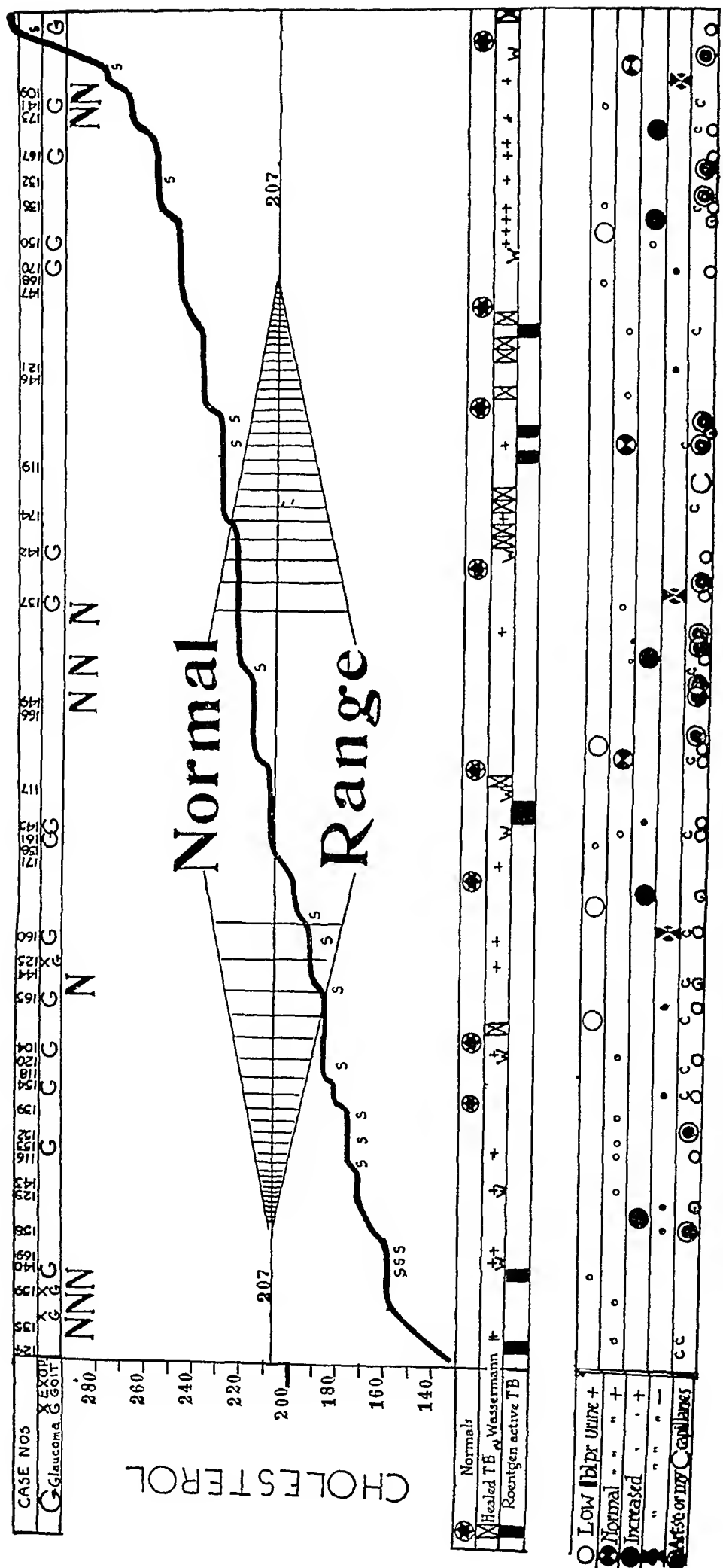


Chart 15—The cholesterol content of the blood of normal persons and patients with various clinical conditions

TABLE 39—*The Results of Examinations Similar to Those in Table 38 of the Twenty Persons with the Lowest Values of Cholesterol*

Individual Number	Cholesterol, Mg	Diagnosis	Reaction to Epinephrine
124	133	Heart disease and arthritis	Vagotonic
108	139	Tuberculosis	Sympathetico tonic
135	145	Nervous	Vagotonic
92	153	Nervous	Sympathetico tonic
1	158	Nervous	Sympathetico tonic
140	158	Tuberculosis, glaucoma	Vagotonic
169	158	Syphilis, Bueiger's disease	Sympathetico tonic
101	158	Sensitized	Sympathetico tonic
153	163	Hodgkin's disease	Sympathetico tonic
96	167	Cardiovascular renal condition	Vagotonic
84	167	Cardiovascular renal condition	Sympathetico tonic
143	171	Pellagra	Sympathetico tonic
85	171	Fever, unknown origin	Vagotonic
116	175	Urticaria	Vagotonic
153	175	Glaucoma	Sympathetico tonic
152	175	Sensitized	Vagotonic
98	175	Cardiovascular renal condition	Vagotonic
139	175	Urticaria	Vagotonic
64	180	Normal (nervous)	Sympathetico tonic
154	180	Glaucoma	
Average	162	Total	10 S, 9 V

REACTIVITY TO EPINEPHRINE THE WHEAL

The average diameter of the wheals due to epinephrine of our group of 100 "normal" men is 19.2 mm, and there appear to be relations to the calcium level, the Kromayer lamp erythema time, the basal metabolic rate, the pulse pressure and the weight/length ratio

TABLE 40—*The Results of Examinations of the Twenty Persons Showing the Smallest Wheals on the Intracutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Mm	Diagnosis	Calcium, Mg	Kromayer Light Erythema Time, Min	Pulse Rate	Carbon Dioxide Combining Power	Ice Reaction Time Seconds
135	12.4	Changes in capillaries, nervous	11.9	75	88	54.5	18
49*	12.4	Cardiovascular renal condition	11	330	60	59.1	15
81*	14	Cardiovascular renal condition	8.4	90	76	57	45
161	14	Glaucoma	9.17	75	88	49.4	12
77*	14	Sensitized	10.8	240	82	60.6	35
144	14.4	Pellagra	9.8	120	92	54.4	10
80*	14.8	Nervous	8	100	64	53.2	30
124	15.2	Arthritis	10.5	90	98	53.7	10
137	15.4	Glaucoma	8.1	130	78	51.9	30
65*	15.8	Cardiovascular renal condition	9.8	180	63	53.1	13
160	16	Glaucoma	10.86	70	68	62.7	10
87*	16	Normal	8.4	90	70	55.4	18
139	16	Urticaria	9.7	120	104	50	8
84*	16.4	Cardiovascular renal condition	10	90	80	53.1	20
143	16.6	Wassermann reaction + + +, pellagra	9.7	110	118	55.4	15
118	16.8	Arthritis	12.2	110	72	54	12
24*	16.8	Healed tuberculosis	11.7	120	78	53.7	20
91*	16.8	Cardiovascular renal condition		150	76	58.9	45
165	16.8	Glaucoma	10	80	110	53.9	5
167	17	Glaucoma	12	120	84	47.9	5
Averages	15.5		10.1	124	82	54.6	18.8

* One of group of 100 "normal" men

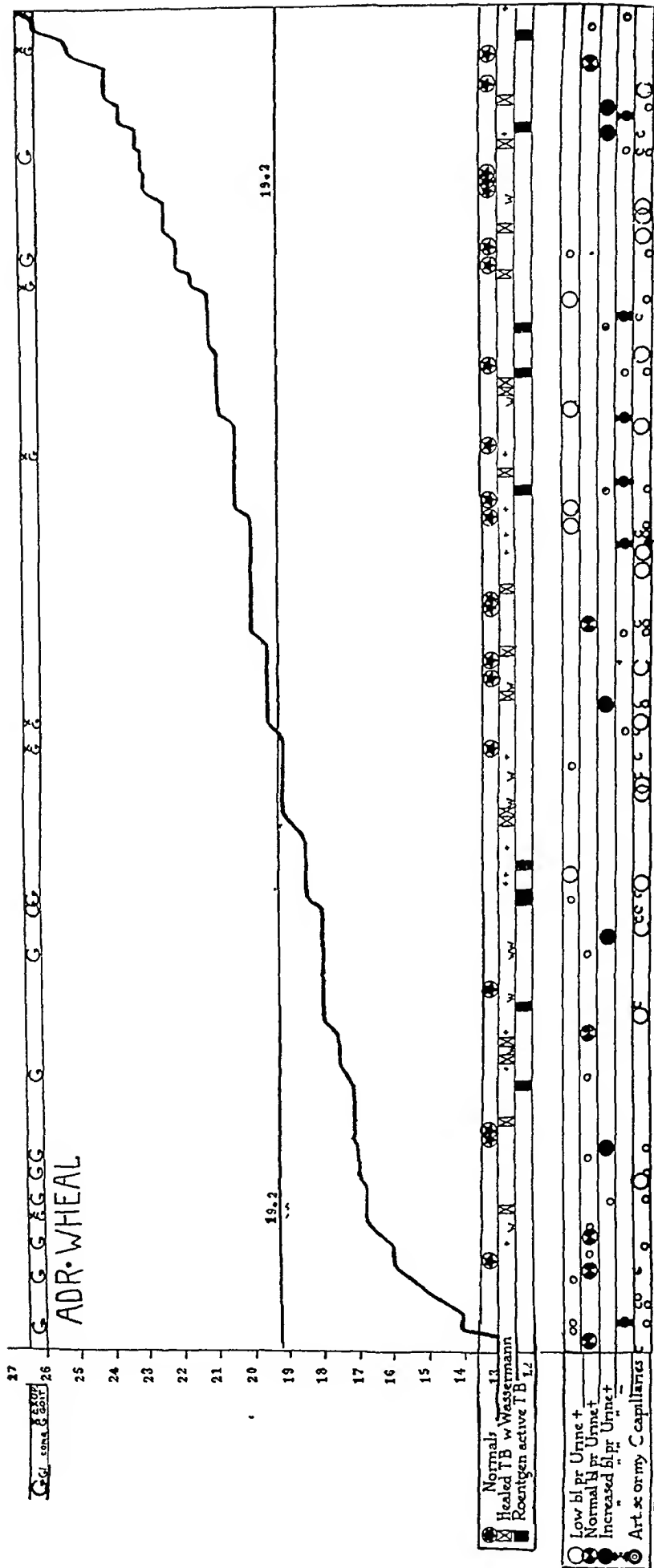


Chart 16—The diameter of the wheal in the reaction to epinephrine of normal persons and patients with various clinical conditions

TABLE 41—The Results of Examinations of the Twenty Persons Showing the Largest Wheals on the Intracutaneous Injection of Epinephrine Hydrochloride

Individual Number	Epinephrine, Mm	Diagnosis	Calcium Mgs	Sugar, Mgs	Kromayer Light Ery thema Time, Mm	Basal Metabolic Rate	Blood Pressure, Systolic	Pulse Pressure	Pulse Rate	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	CO ₂ Combining Power	Ice Reaction, Seconds	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm
121	26	Arthritis deformans	8.9	74	120	+11	148	80	88	Vagotonic	-13	59.8	10	8	0
152	26	Angioneurotic edema	9.8	63	60	+4.8	120	46	80	Vagotonic	-5	63.4	15	9	8
20*	25.2	Tuberculosis	11.4	85	90	+20.4	130	54	80	Vagotonic	+13	62.7	15	10	2.6
50*	24.8	Normal	11.4		180	+21	128	58	67	Sympatheticotonic	+12	64.9	15	10.4	10
11*	24.4	Cardiovascular renal condition	11.2	67	90	+2.7	128	48	76	Vagotonic	10	65	40	15	5
41*	24.4	Normal	9.8	70	75	+15	110	36	64	Vagotonic	+26	58.6	7	6.2	0
40*	24	Changes in capillaries	10.8	56	75	+22	110	46	60	Vagotonic	+6	55.7	40	6.2	0
95*	23.6	Healed tuberculosis	7.8	77	110	+23	110	44	68	Sympatheticotonic	+9	61.6	10	12	6.2
134	23.6	Cardiovascular renal condition	9.9	71	80	-4.4	148	62	78	Sympatheticotonic	-0	54.8	12	19.2	9.6
32*	23.6	Cardiovascular renal condition	9.5	76	75	+22	144	58	74	Vagotonic	+22	54.1	25	9.8	0
21*	23.2	Cardiovascular renal condition	10.2	72	105	+4.3	140	56	72	Vagotonic	0	62.9	25	7.2	2.6
13*	23.2	Healed tuberculosis	12.1	70	90	-4.9	128	60	60	Sympatheticotonic	+13	57.6	38	11.6	12
102*	23.2	Tuberculosis	10.6	62	90	+22	114	44	96	Vagotonic	+11	60.9	40	12.2	0
138	23	Frohlich's syndrome	10.6	83	90	8	122	46	80	Vagotonic		55.2	17	17	6.5
154	23	Glaucoma		71	90	18	194	76	70			56.6	20	26	0
35*	22.8	Normal	8.7	79	75	12.3	108	30	62	Vagotonic	+33	57.6	20	9.2	0
29*	22.8	Normal (bile in urine)	10	76	195	3.5	134	16	76	Sympatheticotonic	+24	60.1	15	7.2	0
4*	22.8	Normal	11.8	94	120	12	114	34	80	Sympatheticotonic	+21	64.3	20	10.2	0
172	22.4	Raynaud's disease	13	76	105	18	108	30	94	Sympatheticotonic	+57		45	18	16
163	22	Glaucoma	9	83	90	2	124	64	64	Sympatheticotonic	+10	73.2	30	18	0
23.8		Averages and totals	10.3	74	99	11.7	128	50	74	8 S, 11 V	+12	60	22.9	12	3.9

* One of group of 100 "normal" men

When we include our entire material and examine the results, some of these correlations are maintained. The differences in calcium levels are not marked, but the Kromayer lamp erythema time is shortened in the group with the larger wheals and the difference between the groups in the CO_2 combining power is well marked, as is that in the ice reaction time (tables 40 and 41).

There are no apparent correlations with blood sugar level, the blood pressure, the pulse pressure or the vascular reactions to epinephrine. The pulse rate is somewhat increased in the group with the smaller wheals.

Chart 16 shows the truly "normal" persons scattered over the entire length of the curve. There appear to be no correlations with the cases of healed or active tuberculosis (roentgenologic evidence) nor with the cardiovascular renal conditions.

REACTIVITY TO EPINEPHRINE THE FLARE

The flare from epinephrine is, as has been shown in chart 1, correlated with a number of other reactions. Thus, it is larger in persons with more calcium, more sugar, higher skin resistance, less globulin and greater vascular reaction to epinephrine. The reactions to thyroxin are not closely related, but the flare due to morphine increases with increase in the flare due to epinephrine.

These observations made on the "normal" group are all confirmed when our averages include the clinical material. In tables 42 and 43, the corresponding results are tabulated for the groups with the greatest and the smallest flares. It will be noted, among other things, that there are more persons with primarily sympathetictonic reactions in the group with the large flares.

Chart 17 indicates that our truly "normal" group, as well as the group showing roentgenologic evidence of healed tuberculosis, are scattered over the entire curve, while more of the group with roentgenologic evidence of active tuberculosis appear at the lower end of the curve. The groups with cardiovascular renal conditions offer nothing that is characteristic, but the group with exophthalmic goiter appears to have smaller flares in contradistinction from the group with glaucoma. The "nervous" persons apparently are more apt to have large flares.

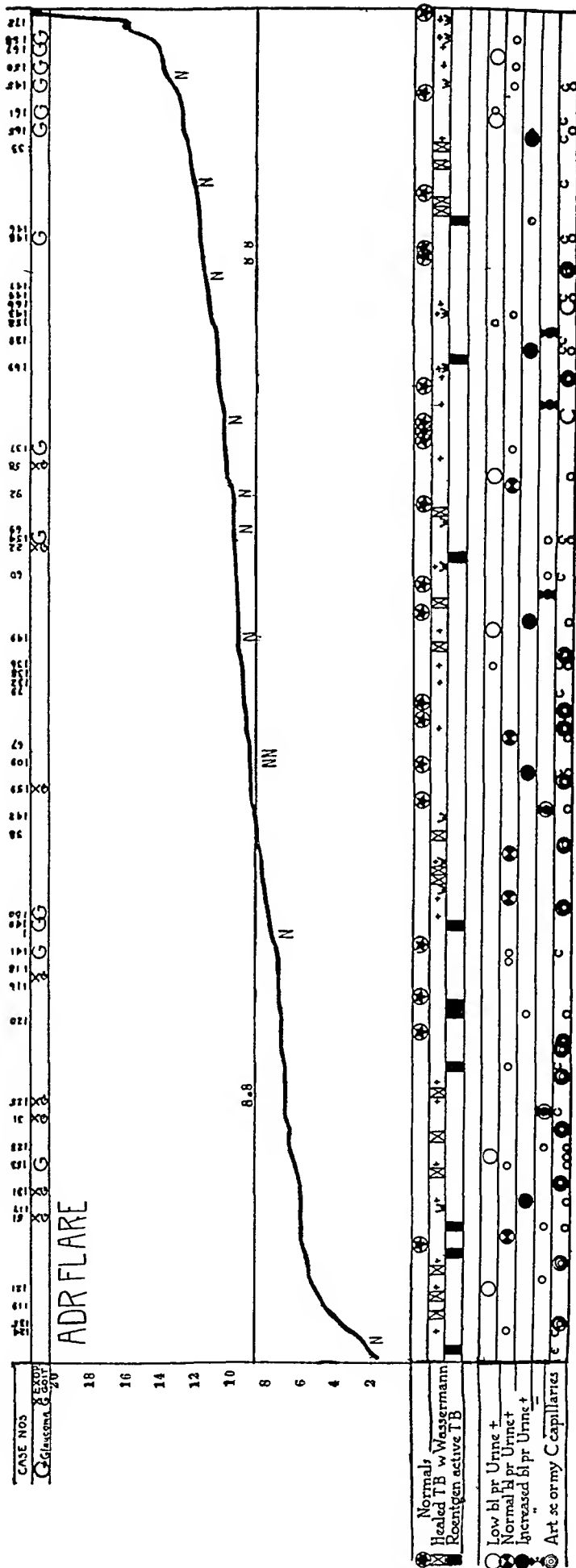


Chart 17—The radius of the flare in the reaction to epinephrine of normal persons and patients with various clinical conditions

TABLE 42—*The Results of Examinations of the Twenty Persons Showing the Smallest Flares Following the Intracutaneously Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Flare, Mm	Diagnosis	Calcium, Mg	Sugar, Mg	Globulin, Mg	Skin Resistance to Electric Current	Blood Pressure, Systolic	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheel, Mm	Thyroxin, Wheel, Mm	Thyroxin, Flare, Mm	Morphine, Flare, Mm
85*	1 8	Fever	10 6	79	33	0 41	110	Vagotonic	+19	17 2	14 2	0	13 8
108*	2 4	Tuberculosis	10 4	63	50	0 44	94	Sympatheticotonic	+ 9	18	14 8	13 2	11
124	2 6	Heart disease, arthritis	10 5	71	40	1 05	122	Vagotonic	+ 2	15 2			6 8
135	3 2	Nervous	11 9	75	45	0 09	120	Vagotonic	-10	12 4	20		2
98*	4	Cardiovascular renal condition	8 8	63	42	0 20	136	Vagotonic	+ 6	20	11 2	0	3
110*	4 2	Healed tuberculosis	12 1	61	28	0 60	110	Vagotonic	- 4	20 8	12	9 4	14 6
47*	5 2	Healed tuberculosis	10 4	72	40	0 13	136	Vagotonic	- 5	21 6	9	0	10 8
130*	5 4	Cardiovascular renal condition	10 4	86	60	0 35	106			20	11 2	0	12 6
121	5 6	Arthritis deformans	8 9	74	30	0 28	148	Vagotonic	-13	26	8	0	8 8
101*	5 6	Healed tuberculosis	9	52	38	0 09	118	Vagotonic	26	19 6	12	10 4	16
107*	5 8	Cardiovascular renal condition	8	60	40	0 33	134	Vagotonic	- 1	20 8	13 4	6 2	11 2
56*	5 8	Tuberculosis	9 8	65	35	0 32	124	Vagotonic	+14	17 2	13 4	7	22 8
94*	6	Normal	8 4	75	37	0 43	134	Vagotonic	20	20	11 2	7 8	14
14*	6 2	Tuberculosis	7 4	55	45	0 08	176	Vagotonic	11	20 8	12	0	10
104*	6 2	Cardiovascular renal condition	11 2	67	37	0 20	128	Vagotonic	0	24 4	15	5	7 2
117	6 2	Syphilitic arthritis	9 2	60	27	0 25	130	Sympatheticotonic	6	19 2	20 2	0	6 2
115*	6 2	Cardiovascular renal condition	7 8	60	60	0 23	148	Vagotonic	- 4	17 2	14 2	8	13 2
81*	6 4	Healed tuberculosis	7 8	77	30	0 39	110	Sympatheticotonic	+ 9	23 6	12	6 2	12 6
95*	6 2	Cardiovascular renal condition	8 4	63	37	0 10	144	Vagotonic	+ 4	14	10	0	15
153	6 5	Glaucoma	9	83	0	0 15	124	Sympatheticotonic	+10	22	18	0	0
5 07		Averages and totals	9 5	68	39 70	308	127 6	4 S, 15 V	+ 4	195	13	4	10 5

* One of group of 100 "normal" men

TABLE 43—*The Results of Examinations of the Twenty Persons Showing the Largest Flares Following the Intracutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Flare, Mm	Diagnosis	Calcium, Mg	Sugar, Mg	Globulin, Mg	Skin Resistance to Electric Current	Blood Pressure, Systolic	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheel, Mm	Morphine, Flare, Mm
37*	12 6	Epilepsy	9 5	83	45	1 75	122	Sympatheticotonic	+ 2	20	22 2
172	16	Raynaud's disease	13	76		0 08	108	Sympatheticotonic	+57	22 4	8 5
168	16	Orthostatic albuminuria	9 4	45	13	0 16	105	Vagotonic	+ 4	18	0
164	14 7	Wassermann reaction +, glaucoma	8 7	65	20	0 23	110	Sympatheticotonic	+14	18	7 5
167	14 2	Glaucoma	12	81	27	0 85	137	Sympatheticotonic	+62	17	9
36*	14 2	Cardiovascular renal condition	12 1	90	33	0 11	104	Vagotonic	22	20 8	18
150	14	Glaucoma	12	82	15	0 22	140	Vagotonic	+ 6	17	9 5
86*	14	Nervous	12 6	94	40	0 36	118	Vagotonic	-12	18 8	19 6
45	13 6	Glaucoma	10 1	70	55	0 35	136	Sympatheticotonic	+43	18	0
41*	13 2	Normal	9 8	70	50	0 26	110	Vagotonic	+26	24	13 8
46*	13 2	Inanition	13 8	61	30	1 7	140	Sympatheticotonic	+15	21 2	16 2
161	13	Glaucoma	9 17	86	20	1 4	108	Sympatheticotonic	+25	14	17 5
65*	13	Cardiovascular renal condition	9 8	65	36	0 80	100	Sympatheticotonic	+30	15 8	19 8
165	13	Glaucoma	10	80	16	0 18	170			16 8	14 5
21*	12 6	Cardiovascular renal condition	10 2	72	20	0 74	140	Vagotonic	0	23 2	13 6
15*	12 6	Healed tuberculosis	12 1	70	20	0 19	128	Sympatheticotonic	13	23 2	12 4
33	21 6	Normal	10	75	42	0 34	116	Vagotonic	- 8	20 4	15 2
24*	12 6	Healed tuberculosis	11 7	81	60	0 19	116	Sympatheticotonic	50	16 8	27 2
173	12 5	Tumor of the cord	10 5	80	6	0 09	106	Sympatheticotonic	23	21	0
80*	12 4	Nervous	8	69	33	1 60	116	Vagotonic	+ 7	14 8	19 2
13 95		Averages and totals	10 7	74	30	0 562	121 5	11 S, 8 V	+20	19	13

* One of group of 100 "normal" men

REACTIVITY TO THYROXIN THE WHEEL

The size of the wheal due to thyroxin, as has been shown in table 1, is related to the inflammatory index, to the potassium level and to the K/Ca ratio, as well as to the amounts of the globulins

When we examine the inclusive material, we find these conclusions confirmed, as becomes evident from a survey of the results of the examinations in twenty cases of the smallest and twenty of the largest wheals (tables 44 and 45)

Chart 18 shows the wide range of the purely normal as well as of the groups with roentgenologic evidence of healed tuberculosis, but also makes evident the fact that the groups with roentgenologic evidence of active tuberculosis are apt to have the larger wheals

The cardiovascular renal groups show no clear-cut relation, unless it is that the arteriosclerotic changes have not been made apparent in those with the small wheals

TABLE 44—*The Results of Examinations of the Twenty Persons Showing the Smallest Wheals Following the Intracutaneous Injection of Thyroxin*

Individual Number	Thyroxin, Mm	Diagnosis	Inflammatory Index	Potassium, Mg	K / Ca Ratio	Globulin, Mg
49*	4.2	Cardiovascular renal condition	11	25.2	2.29	17
116	5	Urticaria	17	19.4	1.94	40
33	5.4	Epilepsy	10	26.1	2.73	45
64*	6.2	Nervous	10	16.6	1.84	22
41*	6.2	Normal	9.1	21.2	2.16	50
40*	6.2	Changes in capillaries	6.6	18.7	1.73	44
90*	6.2	Nervous	7.6	14.5	1.34	33
3*	6.4	Healed tuberculosis	11.1	16.7	1.47	23
24*	6.6	Healed tuberculosis	11.6	24.8	2.12	60
26*	7.2	Syphilis	11	26.6	2.61	35
29*	7.2	Normal (bile in urine)	10.7	23.9	2.39	50
23*	7.2	Healed tuberculosis	11.1	28.6	2.19	
21*	7.2	Cardiovascular renal condition	9	25.6	2.51	20
34*	7.2	Changes in capillaries	7.7	27.7	2.89	25
25*	7.4	Healed tuberculosis	10.6	24.1	2.19	42
36*	7.4	Cardiovascular renal condition	7.2	26.3	2.17	33
39*	7.6	Syphilis	5.8	18	1.91	43
48*	8	Syphilis	9.7	27.6	2.87	40
121	8	Arthritis deformans	11.5	20.2	2.27	30
79*	8.2	Ulcer	5.7	20	1.78	50
Averages	6.75		9.7	22.5	2.17	36.9

* One of group of 100 "normal" men

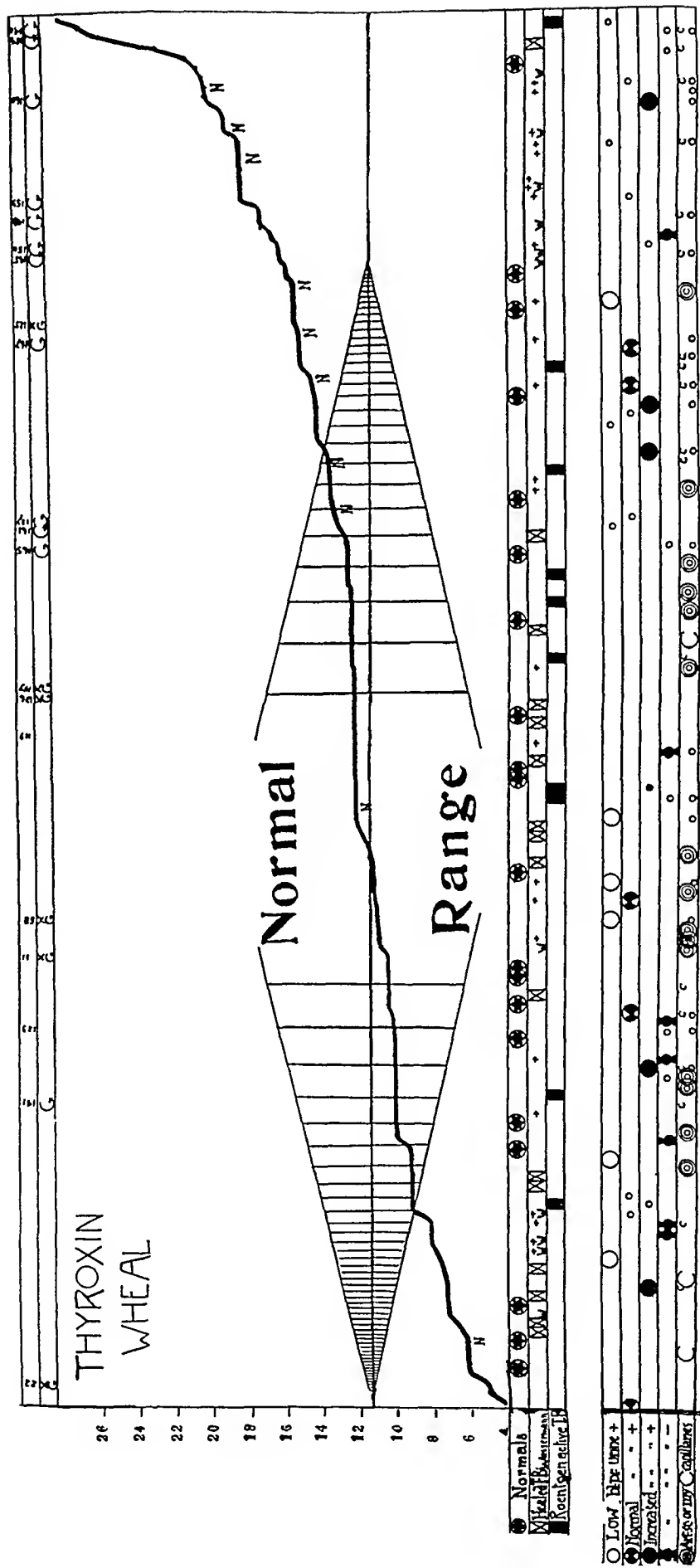


Chart 18—The diameter of the wheal in the reaction to thyroxin of normal persons and patients with various clinical conditions

IV THE PATIENT WITH EXOPHTHALMOS AND THE NERVOUS PATIENT¹

In a previous communication, we called attention to the fact that the blister time of the patient with exophthalmos is considerably shortened, and that the permeability of the capillaries of the skin, as measured by the relative amount of protein in the blister, is markedly increased¹

It is a well known clinical observation that the skin of the patient with exophthalmos is thinner and more transparent than that of a normal person, and vasomotor lability is plainly evidenced by the rapid flushing and pallor. The arterioles, as well as the capillaries, are dilated. The functional status of the skin is one of exaggerated activity involving both the radiation of heat and evaporation. It has recently been shown that the secretory activity of the sweat glands of the skin is controlled by a skin plexus largely independent and locally autonomic, although the sympathetic nerves are commonly regarded as the nerves having to do with secretory functions. We have used the term parasympathetic status to designate this condition of activity of the skin for reasons discussed elsewhere²

Among our group of patients there have been twelve with typical exophthalmos, as well as one patient with hyperthyroidism associated with carcinoma of the thyroid, and one patient who was being treated with thyroid extract (basal metabolic rate +31) following a thyroidectomy. In six of the patients, we were able to carry out a complete reexamination several months after the thyroidectomy.

CLINICAL HISTORIES OF "SYMPATHETICOTONIC" PATIENTS AND PATIENTS WITH EXOPHTHALMOS

CASE 9—A white man, aged 36, had become ill with palpitation and tachycardia fourteen months previous to the examination. He had lost 10 pounds (4.5 Kg). Eight months later, he had a similar attack. Occasionally, he had night sweats. He had a rather coarse tremor. On exertion he showed slight dyspnea. At the time of examination, he had the papular and pustular lesions of acne. The conjunctivae were slightly injected. A few cervical glands were palpated below the angle of the jaw, and there was a light contraction of the superclavicular fossa. The blood pressure was 132 systolic and 86 diastolic. The basal metabolic rate on December 24 was +34, and on December 28 was +49. There was no exophthalmos. In this case, the disease was mild.

¹ In collaboration with Dr. Lindon Seed of the Department of Surgery, University of Illinois College of Medicine.

¹ Petersen, W. F. Permeability of Skin Capillaries in Various Clinical Conditions, *Arch. Int. Med.* **39**: 19 (Jan.) 1927.

² Petersen, W. F., and Muller, E. F. Splanchnoperipheral Balance During Chill and Fever, *Arch. Int. Med.* **40**: 575 (Nov.) 1927.

CASE 11—A white man, aged 46, had been nervous, with tachycardia and sweating for the past eight months. He had a tremor, and was dyspneic. He had been irritable for about a year. There was no exophthalmos. The pulse rate was 80, the blood pressure was 120 systolic and 60 diastolic. His normal weight was 176 pounds (79.8 Kg), at this time it was 136 pounds (61.7 Kg). The neck showed a soft fulness in the region of the thyroid gland. The presence of exophthalmos was questionable. The heart seemed to be heaving somewhat, but no murmurs were apparent. The x-ray diagnosis was myocarditis. The urine was normal. The basal metabolic rate was +42. In this case, the disease was mild.

CASE 16—A white man, aged 33, had been sick for ten months. His illness had begun with nervousness, tremor, fatigue, palpitation and occasional nausea. At the time of observation, the patient was feeling better, but still had some dyspnea. His normal weight was 152 pounds (68.9 Kg), at the time of the examination it was 124 pounds (56.2 Kg). The pulse rate was 90, the blood pressure was 133 systolic and 70 diastolic. He showed no exophthalmos. The thyroid gland was diffusely enlarged. A systolic murmur was heard over the aortic valve. A trace of albumin was found in the urine. The basal metabolic rate was +20. Clinically, the case was debatable. The results of the laboratory examinations were also doubtful. The albumin/globulin ratio was high (56), and there was a possibility of tuberculous activity in the right apex that would account for some of the symptoms.

CASE 22—A white man, aged 58, had become ill, three months previous to examination, with tremor, palpitation, nervousness, loss of strength and excessive perspiration. The blood pressure was 134 systolic and 64 diastolic. There was no exophthalmos. A moderately large diffuse thyroid gland of firm consistency was noted. The urine was normal. The basal metabolic rate was +44. The pulse rate was 100. The x-ray diagnosis was heart, large, mitral lesion (?). In this case, the disease was mild.

CASE 119—A white woman, aged 43, had felt a marked general weakness for two years, she perspired easily. During this time she had lost 20 pounds (9 Kg), despite a good appetite. She had a slight enlargement of the thyroid gland. At the time of the first examination, the basal metabolic rate was +13 and the pulse rate 82. In addition to the endocrine disturbance, she gave some evidence of having arthritis deformans (x-ray diagnosis). No exophthalmos was observed. In this case, the disease was mild.

CASE 31—A white woman, aged 42, began to have a swelling of the thyroid two years previous to examination. At the times of menstruation she had nausea and vomiting with increased hemorrhage. The illness had commenced with nervousness, after the birth of her sixth child, and had been particularly accentuated during her seventh pregnancy. She had diarrhea occasionally, and tremor. She had lost 44 pounds (20 Kg) in the last ten months. Her normal weight was 175. Her weight at this time was 138 pounds (62.6 Kg). She had a nervous breakdown three weeks before examination. The blood pressure was 115 systolic and 75 diastolic. No exophthalmos was observed. The thyroid gland was soft and the right lobe and the isthmus were particularly enlarged. The urine was normal. The basal metabolic rate on January 27 was +73, and on January 31, +44. In this case, the condition was moderately severe.

CASE 51—A white woman, aged 58, had become ill four months prior to examination, with a loss of 50 pounds (22.7 Kg) in weight, nervousness, the sensation of warmth and palpitations. She had vomited occasionally, and had had diarrhea. There was slight exophthalmos and the thyroid gland was moderately enlarged. A tremor was present. The urine was negative. The basal metabolic rate on

February 19 was +67. The blood showed a sugar value of 120 mg, a nonprotein nitrogen value of 32 mg, and a urea value of 17 mg. The Wassermann reaction was negative. In this case, the disease was moderately severe.

CASE 58—A white woman, aged 39, began to have a swelling of the thyroid gland four years prior to examination. Her illness dated back one year to a time when she grew irritable. She perspired freely and had a tremor. Exophthalmos was marked. There had been little loss of weight and the appetite was good. The goiter felt firm. The urine was normal. The basal metabolic rate was +94 on March 23 and +80 on March 24. The Wassermann reaction was negative. The blood sugar was 100 mg. The nonprotein nitrogen was 32 mg. In this case, the condition was moderately severe.

CASE 159—A white man, aged 53, became ill in November, 1925, he felt weak, and lost 45 pounds (20.4 Kg). After that he had periods of nervousness. Exophthalmos and tremor were noted (July, 1927) in the dispensary and a myocarditis was suspected (pulse rate, 96, blood pressure, 124 systolic and 60 diastolic, dyspnea, and diastolic murmur at the base). On August 2, the basal metabolic rate was +42, it was the same in October, 1927, when we made our examination. At this time the patient was improving.

CASE 125—A white woman, aged 29, began to be ill, eleven months prior to examination, with palpitation, weakness, loss of 57 pounds (25.9 Kg) in weight, nervousness and excessive perspiration. The illness in question began with nausea and vomiting. Exophthalmos was present. There was a diffuse, soft enlargement of the thyroid gland. The urine was normal. The basal metabolic rate on July 2 was +58, on July 23, +85, and on July 27, +59. The blood pressure was 170 systolic and 85 diastolic. The pulse rate was 140. This was a severe case.

CASE 126—A white man, aged 21, began to be ill, four months prior to examination, with nervousness, tremor and loss of strength. His normal weight was 157 pounds (72.1 Kg) and he had lost about 20 pounds (9 Kg). He felt weak and perspired freely. The blood pressure was 142 systolic and 60 diastolic, the pulse rate was 112. There was moderate exophthalmos and diffuse general enlargement of the thyroid. The urine was normal. The basal metabolic rate on July 2, 1927, was +25. The sugar was 83 mg, the nonprotein nitrogen, 37 mg. This was a severe case.

CASE 131—A white woman, aged 59, began to be ill, sixteen months prior to examination, with nervousness. She had a nervous breakdown one year before examination, together with palpitation and the feeling of warmth, occasional vomiting and diarrhea. Her loss in weight had been 80 pounds (36.3 Kg), i.e., from 204 to 118 pounds (92.5 to 53.5 Kg). There was a moderate enlargement of the thyroid gland and slight exophthalmos. The urine showed a trace of albumin. The basal metabolic rate on July 15 was +88. In this case, the disease was severe.

CASE 57—A white woman, aged 38, commenced being ill with palpitation six months before examination. For three months prior to examination she had been nervous and weak, had perspired readily and had lost 40 pounds (18.1 Kg). She had been nauseated for about two months. Exophthalmos was not marked. The urine was normal. The basal metabolic rate was +150. A goiter had been removed three months previous to examination. About Jan. 1, 1927, the patient began to feel weak and noticed lacrimation, impaired vision and slight swelling of the face. The patient returned on March 7 with some evidence of myxedema. She was given a course of treatment with thyroid extract. Our examination was made on February 22, at this time, the effect of the thyroid extract was apparent in a basal metabolic rate of +31.

TABLE 1—Results of Correlative Examinations

	Individual Number	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg	Potassium, Mg	K / Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Wassermann Reaction	Kromayer Light Frythem's Time, Hours	Basal Metabolic Rate	Skin Resistance	Muscle Reaction, Ma	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure x Pulse Rate, %	CO ₂ Combining Power	Endothelial Reaction
Mild	9	5.5	71	13	11.5	23.5	2.04	88	1.7		2	+49	0.75	2.2		Systolic	Diastolic		+28	+46	61.5	+
	11	5	70	14	10.9	24.1	2.21	82	3		3	+42	0.14	5.5		140	70	96	+6			
	16	5	80	16	11.4	21.6	1.9	75	5.6		2.25	20.8	0.11	1.9	+	124	74	108	+9	58.1		
																150	68	88	22	35	55.3	
	22	6	73	12	12.1	18.2	1.5	91			1.25	44	0.17	3		144	74	92	+31	+44	52	+
Mod severe	119	6.45	58	8.5	9	18.7	2.1	75	1.7		1.25	34	0.08	3		142	82	98	+13	+24	55.4	
	31	5.5	70	12.7	9.5				0.28			+73				115	75	114			49.2	
	51	5	77	14	10	25.8	2.58	91	5.4	Did not appear	1.10	+67	0.13	5		124	50	104	25	35	55	
	58	5	75	15	12	25.9	2.5	120	1.2		1.10	+43	0.10			144	60	127	+2	+5	52.9	
Severe	159	5	69	14	8.23	17.9	2.17	71	No globulin		1.18	+46	0.22		Trace	132	68	80	+17	+30	54.8	
	125	6	74	12	11.5			81	0.66		1.5	59	0.48	1.5		170	85	140			55.5	+
	126	6			9	18	2	77	2.3		?	105	0.20	0.8	?	148	66	90	20	23	60.6	
	131	5	77	15.4	9.6	18	1.87	113	1		2	+88	0.21		+						44.6	
	57	7.75	80	10.3		24.7		92	2.3		2.15	+31	0.55			94	61	78	+34	+50	60.2	
	123	9.25	74	8	9.2	20	2.17	81	2.4		?	+48		2.2	+	165	100	81	-3	+5	52.4	+
Av	5.89		72.9	12.68	10.3	21.4	2.09	79.7	2.6		1.77	+48	0.25	2.79		146	72	100	+19	+33	54.5	

TABLE 2—Comparison of the Averages of the Reactions of a Group of Patients Men, a Group of "Sympatheticotomic" Persons

Group	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Kromayer Light Frythem's Time, Min	Ice Reaction Time, Seconds	Skin Resistance	Intracutaneous Reactions to Pharmacologic Substances							
							Epinephrine Wheel (Diameter, Mm)	Epinephrine, Flare (Radius, Mm)	Morphine, Wheel (Diameter, Mm)	Morphine, Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffien, Wheel (Diameter, Mm)	Caffien, Flare (Radius, Mm)
20 normal men	6.8	62	9.3	110	14.5	0.33	21	9.36	11.7	16.3	11.6	5.45	17.9	3
6 patients with exophthalmos, before operation	5.3	75	14	110	19	0.13	21.9	8.4	10.7	13	10	7.6	13.6	0
after operation	7.4	62	10.7	70	9	0.23	20	12.5	13.5	7	17	13	16	6.5
10 "sympatheticotomic" persons	7.7	69.1	9	103	23	0.41	19.4	9.4	10.6	13.2	12	4	21.2	2.6
12 "nervous" patients	7.5	69.1	9.2	112	20.4	0.79	18.3	10	11.6	14.6	14	6.8	18.6	3.8

of Patients with Exophthalmic Goiter

Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine Wheel (Diameter, Mm)	Epinephrine Flare (Radius, Mm)	Morphine Wheel (Diameter, Mm)	Morphine Flare (Radius, Mm)	Thyroxin, Wheel (Diameter, Mm)	Thyroxin, Flare (Radius, Mm)	Caffein, Wheel (Diameter, Mm)	Caffein, Flare (Radius, Mm)	Diagnosis	
Asthenic		+	Granulation		27	200											
Asthenic	Healed	0	Normal		46	195											Myocarditis (x ray diagnosis)
Asthenic	?	+	Normal		7	33				7.2	18						Possibility of active tuberculosis of right apex (healed tuberculosis) (x ray)
Nervous	Healed	+	+		5	38		26.4	10.2	15	10	5	1	7	0		Heart large, mitral lesion (x ray)
Nervous			Normal		10	43	266	330	24	5	12	11.2	12	7	17.4	5.6	Arthritis deformans (x ray)
Nervous		0	Normal	(40)	42	200		21.6	7	9	13.6	7.2		7.4	3.6		
Sthenic			Normal	5	58	195		19.2	6.2	11	13.4	9.2	4.8	9			
Asthenic			Normal	25	29	188		19.6	10.4	9.8	13.8	11.2	6.8	12			Myocarditis (x-ray) ?
Sthenic				7	53	196	158	25	9	6.4	3.5	12	0	15	0		
Sthenic	Healed	+	Normal	18	29		190	22.4	7	10.4	9	15.2	17	26.4			Myocarditis (right lung, increased fibrosis) (x ray)
Sthenic			Normal	5	21	174	190	19.6	7			12		32.4			
Sthenic		+	Normal	7	59	177	147	16.8	6.2	12	8.8	10.4	6.2	10			
Sthenic		+	Normal	6	39	221		18.4	7.4	12.4	15.4	12.2	14	20.2	5		Hyperthyroidism on extract after operation
Sthenic		+	Normal	8	63	263	171	20	6.8	11.2	10.2	10	11.2	19.2			Hyperthyroidism with carcinoma of the thyroid gland, ioditis
				86	42	208	197.6	21.2	7.5	10.6	11.5	10.6	6.4	16	2.8		

with Exophthalmos with the Averages of the Reactions of a Group of Normal and a Group of "Nervous" Persons

Blood Chemistry					Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure x Pulse Rate, %	Blood Pressure		Pulse Rate	Basal Metabolic Rate	Weight/Length Ratio	Age
Calcium, Mg	Potassium, Mg	K / Ca Ratio	CO ₂ Combining Power	Sugar, Mg			Systolic	Diastolic				
9.7	20.3	2.1	57.6	72.8	+19.6	+28.6	116	70	68	+5	224	40.2
11.3	23.1	2.04	54.1	91	+17	+25	142	70	110	+46	200	39
9	18.5	2.04	63	71	+9	+17	123	70	85	+7.6	240	39
10.8	18.83	1.74	54.6	72.6	+21.4	+26.7	123	70	80	+10.4	206	52
10.8	18.8	1.74	57.8	76	+10.5	+22.5	120	64	80	+8.5	198	33.6

CASE 123—A white woman, aged 68, had had a carcinoma of the uterus fifteen years previously, which was removed. Four years prior to the examination, she had had a malignant tumor of the thyroid gland, which she subsequently had had removed three times. At the time of the examination, she suffered from dyspnea caused by the growth, considerable loss of weight during recent months and some evidence of hyperthyroidism. The roentgen examination of the chest revealed a large heart and aortitis. The blood pressure was 182 systolic and 100 diastolic. The tumor was regarded as inoperable. No exophthalmos was noted. The symptoms in this case were mild.

In table 1, we have grouped the results of the various examinations carried out in these cases, the first five cases being mild, the next four moderately severe and the last group severe.

For purposes of comparison with the normal, we present in table 2 the averages for twenty normal persons, six patients with exophthalmos before and after operation, ten "sympatheticotonic"³ patients and twelve "nervous" persons.

In table 3, the individual reactions of six patients with exophthalmos before and after operation are shown.

COMMENT

Blister Time—As previously shown,² the cantharides blister time is markedly shortened in the patients with exophthalmos. We presume that this is, in general, due to the increased parasympathetic status of the periphery. Following removal of the thyroid gland, the blister time is lengthened. Seemingly, the blister time is not necessarily related to the basal metabolic rate, for in case 123 (carcinoma with hyperthyroidism, basal metabolic rate +48), the blister time was not shortened, nor was it in case 57 (therapeutic hyperthyroidism following insufficiency due to thyroidectomy, basal metabolic rate +31). On the other hand, in case 22, thyroidectomy was followed by a considerable shortening of the blister time, despite the lowering of the basal metabolic rate to +3. The patient in this case gave other evidence of continued autonomic disturbance.

Permeability of Capillaries—The relative amount of protein present in the blister is high in the case of exophthalmic goiter. We regard this as evidence of increased capillary permeability.⁴ It will be observed that both the "sympatheticotonic" and the "nervous group" approach the patients with exophthalmos in this respect. Following thyroidectomy, permeability is diminished in all cases. Both the hyperthyroidism associated with carcinoma and that following treatment with thyroid

3 Petersen, W. F., and Levinson, S. A. Arch Int Med 42:256 (Aug.) 1928.

4 Petersen, W. F., and Willis, D. A. Capillary Permeability and Inflammatory Index of Skin in Normal Person as Determined by Blister, Arch Int Med 38:663 (Nov.) 1926.

extract are associated with high permeability. The increase in permeability seems directly related to thyroid activity in some way, but not necessarily with the factor that is responsible for the increase in basal metabolic rate. In case 16 (in which the basal metabolic rate did not change following thyroidectomy) the capillary permeability diminished. On the other hand, in patient 119 (arthritis deformans, adenoma of the thyroid, basal metabolic rate +34) the permeability was low, but the patient had some of the symptoms of hyperthyroidism.

Calcium—Contrary to the observation of Kylin⁵ and Leicher,⁶ we have, in general, found an increase in the calcium of the serum, the average for our twelve cases is 10.4, and for the six cases studied before and after operation the respective values are 11.3 and 9. Our results agree with those of Jacobsohn and Rothschild.⁷ Herzfeld and Neuburger⁸ reported conflicting results. Whether or not the high calcium level is partly responsible for the sympatheticotonic effects we cannot state. It has been previously demonstrated that calcium is lost from the body during treatment with thyroid (Bolaffio, Tedesco and Falta⁹).

Potassium and the K/Ca Ratio—As the potassium is increased proportionally to increase in calcium, the K/Ca ratio remains approximately at 2. After thyroidectomy, the potassium level drops with the calcium level and the ratio remains constant. At the operation, both upper parathyroids were removed, with approximately two thirds of the thyroid tissue.

Albumin/Globulin Ratio—In severe cases there is a considerable increase in serum globulin. We doubt whether this is a specific effect, because it occurs so frequently in severe intoxications. Following thyroidectomy, the albumin again increases. In sympatheticotonic persons the globulin shows a slight increase.³

Neither the change in the calcium and the potassium levels nor the change in the albumin/globulin ratio is due to changes in the concentration of the serum, for we find that the serum proteins are, if anything, more concentrated after the thyroidectomy. Similar changes were reported by Frowein.¹⁰

Kromayer Light Erythema Time—In patients with exophthalmos, the time of the appearance of the erythema following application of the Kromayer light is somewhat shortened following thyroidectomy. This

5 Kylin, E. Acta med. Scandinav., 1928, suppl. 19, p. 1.

6 Leicher, H. Deutsches Arch. f. klin. Med. **141** 85, 1923.

7 Jacobsohn, M., and Rothschild, F. Ztschr. f. klin. Med. **105** 417, 1927.

8 Herzfeld, E., and Neuburger, J. Munchen med. Wchnschr. **71** 1324, 1924.

9 Bolaffio, Tedesco and Falta. Wien klin. Wchnschr. **22** 1059, 1919.

10 Frowein, W. Ztschr. f. d. ges. exper. Med. **24** 162, 1921.

is even markedly apparent in one patient (no 51) in whom no erythema appeared before operation, but after operation it appeared in 100 minutes

Reaction to Ice—The shortness of the Kromayer light erythema time is paralleled by the rapidity of the appearance of erythema following the local application of ice. Possibly, the lessening of the peripheral sympathetic tonus accounts for the more rapid reaction, although the so-called "parasympathetic" person shows little difference from the "sympathetic" person in this reaction.³

Resistance of Skin to Electric Current—A rather striking difference exists in the resistance of the skin to electric current. This is somewhat reduced in exophthalmic goiter (a similar observation was made by Richter¹¹), but after operation it returns to normal. Whether this response is modified by the enhanced sweating of the patient with exophthalmos we leave undetermined. Lueg and Grassheim¹² studied the electric condensation values of the skin. These, too, are altered in exophthalmic goiter.

CO₂ Combining Power—The CO₂ combining power is slightly lowered before, and returns to a supernormal level after thyroidectomy. This is in agreement with the determinations of Hollo and Weiss,¹³ Morros¹⁴ and Walinski and Herzfeld.¹⁵

Intracutaneous Reactions to Pharmacologic Substances—The reactions of the skin to pharmacologic substances are of some interest. As compared with the reaction of a normal person, the wheal due to epinephrine hydrochloride in a patient with exophthalmos is somewhat increased and the flare lessened, the wheal and the flare due to morphine are diminished, the wheal due to thyroxin is diminished, but the flare is increased, the wheal and the flare due to caffeine are diminished. After operation there is a distinct reversal in the reaction to epinephrine in that the wheal is again diminished, but the flare increased. In the reaction to morphine, the wheal is again increased, but the flare is decidedly contracted, the same being true in the reaction to thyroxin. That these changes are associated with hyperthyroidism and not necessarily with the associated autonomic changes which are by some assumed to underly the pathologic alterations seems indicated from the reactions

11 Richter, C. P. Electrical Skin Resistance, Diurnal and Daily Variations in Psychopathic and in Normal Persons, *Arch Neurol & Psychiat* **19** 488 (March) 1928

12 Lueg, W., and Grassheim, K. *Klin Wchnschr* **7** 647, 1928

13 Hollo, I., and Weiss, S. *Klin Wchnschr* **3** 163, 1924

14 Morros, J. S. *Arch Endocrinol* **4** 279, 1926

15 Walinski, F., and Herzfeld, E. *Munchen med Wchnschr* **73** 2153, 1926

TABLE 3—*The Results of Correlative Studies of Six Patients with Exophthalmos Before and After Thyroidectomy**

Case	11	16	22	51	58	125	Averages
Blister Time, Hours							
Before operation	5	5	6	5	5	6	5.3
After operation	7.5	5.5	2.5	10	6.5	12	7.4
Permeability of Capillaries, per Cent							
Before operation	70	80	73	77	75	74	75
After operation	66	66	66	60	58	60	62
Inflammatory Index							
Before operation	14	16	12	14	15	12	14
After operation	8.5	12	25	6	8	5	10.7
Kromayer Light Erythema Time, Min							
Before operation	180	135	75	Did not appear	75	90	110
After operation	55	60	66	100	90	66	70
Reaction to Ice, Seconds							
Before operation	9	7	5	10	25	18	10
After operation	25	7	10	10	9	10	9
Skin Resistance							
Before operation	0.11	0.11	0.17	0.13	0.1	0.48	0.13
After operation	0.23	0.5	0.11	0.11	0.18	4.1	0.23
Endothelial Reaction							
Before operation	—	—	—	—	—	+	Unchanged
After operation	—	—	—	—	—	+	—
Epinephrine, Wheal, Mm							
Before operation			26.4	19.2	19.6	22.2	21.9
After operation	15.2	17	18	20	18	23	20
Epinephrine, Flare, Mm							
Before operation			10.2	6.2	10.4	7	8.4
After operation	18	12.5	13	12.5	15	10	12.5
Morphine, Wheal, Mm							
Before operation		7.2	15	11	9.8	10.4	10.7
After operation	13	12	11	17.5	12	15	13.5
Morphine, Flare, Mm							
Before operation		18	10	13.4	13.8	9	13
After operation	14.7	7.7	10.15	8.75	0	10.7	7.5
Thyroxin, Wheal, Mm							
Before operation			5	9.2	11.2	15.2	10
After operation		18	9	22		24	17
Thyroxin, Flare, Mm							
Before operation			1	4.8	6.8	17	7.6
After operation		0	0	0		4.5	1.3
Caffein, Wheal, Mm							
Before operation			7	9	12	26.4	13.6
After operation	9	21	9	21	16	25	16
Caffein, Flare, Mm							
Before operation			0	0	0	0	0
After operation	0	0	0	10.5	0	2.5	6.5
Serum Protein, per Cent							
Before operation	7.2	7.2	7.76	7.85	8.25	9.13	7.92
After operation	8.7	6.12	8.7	7.41	8.38	9.76	8.18
Calcium, Mg							
Before operation	10.9	11.4	12.1	10	12	11.5	11.3
After operation	8.54	9.65	9.81	?	7.76	9.6	9.07
Potassium, Mg							
Before operation	24.1	21.6	18.2	25.8	25.9	?	23.1
After operation	17.75	20.7	20.4	19.21	13.49	19.7	18.5
K / Ca Ratio							
Before operation	2.21	1.7	1.5	2.58	2.15	?	2.04
After operation	2.08	2.14	2.08	?	1.74	2	2.04
CO ₂ Combining Power							
Before operation		55.3	52	55	52.9	55.5	54.1
After operation	57.5	66.2	74	62.2	50.1	62.6	63
Albumin / Globulin Ratio							
Before operation	3	5.6	?	0.54	1.2	0.66	2.2
After operation	No globulin		7.3	4.5	1.9	2.7	
Sugar, Mg							
Before operation	82	81	91	91	120	81	91
After operation	61	67	71	90	71	67	71
Reaction to Epinephrine							
Increase in Pulse Pressure, per Cent							
Before operation	+0.66	+27	+31	+25	+2	?	+17
After operation	14	10	15	7	0	9	+9
Increase in Pulse Pressure × Pulse Rate, per Cent							
Before operation	9	35	41	35	5	?	25
After operation	23	17	35	16	0	13	17
Pulse Rate							
Before operation	108	88	92	104	127	140	110
After operation	84	72	80	74	90	100	85
Blood Pressure, Systolic/Diastolic							
Before operation	124/74	150/68	144/74	124/50	144/69	170/85	142/70
After operation	118/78	134/70	124/66	105/77	130/72	126/80	123/74
Pulse Pressure							
Before operation	50	62	70	74	75	85	72
After operation	40	64	58	27	58	46	49
Weight/Length Ratio							
Before operation	195	195	233	195	188		200
After operation	234	186	288	270	222	210	240
Basal Metabolic Rate							
Before operation	42	20	44	67	43	59	46
After operation	-3	20	3	-12.6	16.5	21	7.6

* The determinations before operation are placed in the upper line and those after operation in the lower line of each bracket

of the skin in patient 123, which, in general, agree with the observations of the other patients with exophthalmos. This particular patient was suffering from carcinoma of the thyroid gland and not from true exophthalmic goiter, there being presumably no underlying or preceding autonomic disturbance.

PREOPERATIVE AND POSTOPERATIVE REACTIONS

When one examines table 3 showing the reactions before and after thyroidectomy, it becomes apparent that a dissociation of certain of the reactions exists.

In case 16, for instance, thyroidectomy was not followed by clinical improvement. The basal metabolic rate remained unchanged ($+20$), the weight diminished, the patient felt weak and a moderate tremor persisted. It will be noted that the blister time remained practically unaltered, as did the time of the reaction to ice.

The reaction of the skin to Kromayer light, the resistance to electrical current and the reaction to morphine followed the typical courses, the capillary permeability diminished and all the chemical and cardiac reactions returned toward the normal.

In case 22, on the other hand, the basal metabolic rate was lowered, and the weight of the patient increased, nevertheless, some of the reactions of the skin showed a distinct abnormality. Thus, the blister time was short, the resistance of the skin to electric current was diminished, and the reaction to morphine was reversed, the reaction to ice was prolonged and the reaction to the Kromayer light was unaltered. The permeability of the capillaries, however, showed normal diminution. Chemically, the only deviation was an increase in potassium instead of a diminution. Clinically, this patient improved.

It seems obvious that one cannot make merely an augmented secretion from the thyroid responsible for all alterations in these autonomic reactions, because if this were the only factor, all of them should return toward the normal after operation, while, as may be observed, there is sometimes a distinct difference in the reactions—for example, in one case the return of the basal metabolic rate to normal, and in the other a persisting increase in the rate.

If one now examines table 2 and compares the results of the examinations of the normal persons with the results of the examinations of the group with exophthalmos before and after operation, it becomes evident that, despite the restoration of weight, the normal basal metabolic rate and the relief of clinical symptoms, decided alterations of the reactions of the skin are still manifest. Thus, the resistance of the skin to electric current remains low, the ice reaction time and the Kromayer light erythema time are short, the red flare of the reaction to epinephrine is increased, while that of the reaction to morphine is diminished, the wheal in the reaction to thyroxin is

increased while the flare is diminished, and in some cases, the flare in the reaction to caffeine seems also increased

CLINICAL HISTORIES OF THE NERVOUS PATIENTS

In the nervous group, our material consists of four persons from the so-called "normal" series, three medical students and a small number of persons studied in the Research Hospital. We have not sought to examine a large series of neurasthenic persons, but have merely grouped the persons who came under observation in the routine study in whom nervousness played a large rôle in the symptom complex (table 4)

CASE 80—An electrician, an American, aged 29, had a distinct tremor and felt nervous. The onset had followed an explosion in a mine in 1924. He had had urticaria in 1922. He was a moderate smoker.

It is to be noted that the capillaries were very permeable, the calcium level was low, potassium levels were low, as was the K/Ca ratio, the capillaries of the skin showed some granulation, the flares about the sites of the intracutaneous injections of pharmacologic substances were wide, the reaction to ice was delayed and faint, the resistance of the skin to electric current was high, the erythema resulting from the application of the Kromayer light was marked.

CASE 92—A medical student, Jewish, aged 22, was nervous, sweated easily and had an occasional tremor. He suffered from lassitude and inability to concentrate. He had a bowel movement once or twice a week.

It is to be noted that the capillaries were very permeable, the calcium level was low, while the K/Ca ratio was high, the reaction to epinephrine was strongly sympathetotonic, the flares of the reactions to pharmacologic substances were all wide, and the reaction to the Kromayer light was faint.

CASE 135—A tailor, Jewish, aged 29, felt nervous and weak, and had had some night sweats and some loss of weight (12 pounds [5.4 Kg.] in one year). The basal metabolic rate was +17. This patient was under observation in the Research Hospital for possible exophthalmic goiter.

It is to be noted that the capillaries showed increased permeability, the K/Ca ratio (18) was somewhat lowered, the globulins were increased, occasional granular casts were observed in the urine, the capillaries of the skin showed evidence of a beginning granulation and beading, the reaction to epinephrine was "vagotonic", the flares of the pharmacologic skin reactions were diminished, and there were roentgenologic evidences of a probably healed tuberculosis.

Of these three cases, therefore, only the third gave evidences of organic disturbances (granular casts), but in all of them there was high permeability of the capillaries, as well as an alteration of the calcium level or the K/Ca ratio.

In the next four cases, a moderate increase of capillary permeability was shown.

CASE 5—A housewife, Jewish, aged 48, the wife of patient 6, had vague pains all over the body, and was nervous.

It is to be noted that the calcium level was high, but the K/Ca ratio was within normal limits, there was a trace of albumin in the urine, and the heart and aorta appeared large on roentgen examination

CASE 109—A spinster, American, aged 42, became weak after unilateral ovariectomy fifteen years prior to examination. Following this, she was nervous, had palpitation, perspired excessively and spent much time in bed because of weakness. One sister had hyperthyroidism.

It is to be noted that the potassium level and the K/Ca ratio were outstandingly low, the basal metabolic rate of +55 was questionable, the test being unsatisfactory because the patient was extremely nervous, the pulse rate was increased, the CO₂ combining power was low, the blood cholesterol level was high,

TABLE 4—The Results of Correlative Exam

Individual Number	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg	Potassium, Mg	K / Ca Ratio	Sugar, Mg	Albumin/Globulin Ratio	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance	Muscle Reaction, Ma	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure x Pulse Rate, %
80	6	91	15.1	8	13.7	1.7	69	2		16.5	+13	16	3.8		Systolic	Diastolic			
92	9	83	8	8.4	19.5	2.32	67	2.8		1.5	-0.8	0.57	2		116	68	64	+7	+12
135	6	84	14	10.8	19.6	1.81	75	1.2		1.25	+17.6			+ Casts Albumin, trace	110	60	72	+46	+70
5	5	72	13	11.0	25.7	2.16	72.7	1.5		1.25		0.21	3.2		120	60	88	-10	-10
															182	92	76		
109	6	72	12	10.8	16.2	1.5	67	2		1.35	+35	0.47			100	60	88	+3	+16
2	7	69	9.8	12.9	26.1	2.02	74.2			3.5	-11	0.1			100	60	100		
1	8	68	8.5	12.1	24.9	2	118	2		5	+7	1			132	74	80	+35	+52
90	9	60	7.6	11.4	14.5	1.34	68	2		1.75	-8.3	0.44	4		122	54	67	+17	+40
86	15	58	3.8	12.6	15.9	1.26	94	1.5		1.75	+6.4	0.36	1.8		118	60	74	-12	-12
46	6	59	10	13.8	17.4	1.24	61	2.3		1.15	+13	1.7	2		140	82	76	+15	+37
149	10	54	5.4	10.1	17.4	1.72	82	?		1	+5	0.95			110	62	72	+10	-22
69	4	51	12.7	9.6	16	1.66	70	2.7		2	+4	1.9	2		140	48	84	0	-8
6	6.25			10.5	18.9	1.8	70.2	1.86	+	1.25	+29.5	0.3	4	Albumin, trace	120	60	72		
Ave	7.5	69	9.2	10.8	18.8	1.74	76	1.98		1.87	+8.5	0.79	3.5		120	64	80	+10.5	+22.5

the wide flare of the reaction to thyroxin was the only abnormality of the intracutaneous reactions, and the reaction to the Kromayer light was faint

CASE 2—A school boy, American, aged 12, had vasoneurosis and epilepsy. He showed active cardiac reflex, and marked mottling of the skin due to areas of vasoconstriction and vasodilatation. This patient is not to be considered as comparable with the others of the group, but has been, nevertheless, included because of the general interest of his case.

It is to be noted that the calcium level was high and the K/Ca ratio normal, the Kromayer light erythema time was prolonged, the basal metabolic rate was low, the resistance of the skin to electric current was low, and the pulse rate was high. Microscopic examination of the capillaries of the skin showed marked dilatation.

CASE 1—A medical student, Jewish, aged 23, was out of school because of a nervous breakdown. He had a tremor and felt weak.

It is to be noted that the calcium level was high, but the K/Ca ratio was normal, the blood sugar level was high, the Kromayer light erythema time was delayed, the resistance of the skin to electric current was high, the reaction

to epinephrine was strongly positive, and the flare of the reaction to thyroxin was increased

The remaining six patients had low capillary permeability

CASE 90—A mail sorter, American, aged 30, was nervous (said that he got "rattled easily") He was sensitive to venipuncture

A low K/Ca ratio was the only outstanding abnormality

CASE 86—A dentist, American, aged 50, had a "breakdown" four years prior to examination He was suffering from alcoholism, was nervous, had lost his practice and was "down and out" Occasionally, he worked as a janitor He had always been the most nervous one of his family His mother had exophthalmic goiter He had had angioneurotic edema when a student in 1900

Examinations of a Group of Nervous Persons

CO ₂ Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg	Epinephrine Wheal (Diameter, Mm)	Epinephrine Flare (Radius, Mm)	Morphine Wheal (Diameter, Mm)	Morphine Flare (Radius, Mm)	Thyroxin Wheal (Diameter, Mm)	Thyroxin Flare (Radius, Mm)	Caffien Wheal (Diameter, Mm)	Caffien Flare (Radius, Mm)
53.2		Sthenic		+	Slight granulation	30	29	212	222	14.8	12.4	12.4	19.2	13.1	9	16.2	7
56.8		Sthenic		+	Normal	20	22	210	158	20.4	10.2	11.8	17	15.2	7.6	10	10
63.9		Sthenic Large	Healed Healed	+ 0	+ Normal	18	26 48	183 210	145	12.4	3.2	8.2	1.6	20.2	0	25	0
51.4		Asthenic			Normal	25	42	140	267	17.4	9	9	7.2	12	9.4	16.2	0
55.6		Asthenic			Dilated												
62.1					Normal	25	23	202	158	20	8	12.4	16	13.2	9.6	12.2	0
57.9		Asthenic	0		Normal	10	30	192	222	15.4	11.6	10.4	20.2	12.2	0	27.4	0
55		Sthenic			Normal	25	30	176	185	18.8	14	11.8	19.6	15.4	12.4	14.2	0
56.2		Asthenic		+	Urinary disturbance	15	29	168		21.2	13.2	15	16.2	12.2	11.2	25.2	9.2
65.1		Sthenic		+	Normal	15	35	209	215	20	9.6	15	7.4	19	0	20	10
54.8		Asthenic	Healed	+	Normal	20	22	160		21.2	10	12.2	22	14.1	10.2	30.4	12.6
61.1		Asthenic		0	Normal		49	300									
57.8						20.4	33.6	198	196	18.3	10	11.6	14.6	14	6.8	18.6	3.8

It is to be noted that he had a prolonged blister time, a low K/Ca ratio, a high sugar level, a vagotonic reaction to epinephrine, and increased flares at the sites of injection of pharmacologic substances (except caffeine)

CASE 46—A carpenter, American, aged 29, a poorly developed person (from insufficient nutrition), fainted on venipuncture He was nervous and had headaches frequently This person died a few months later at the Cook County Hospital from bronchopneumonia

It is to be noted that he had a high calcium level with a low K/Ca ratio, a high resistance of the skin to electric current, relatively high blood pressure, with some evidence of abnormality of the capillaries of the skin, and an increase in the flares of the reactions to all the pharmacologic substances

CASE 149—A plumber, American, aged 35, was nervous, had some night sweats and had lost some weight Recently, he had been in financial difficulties His mother had high blood pressure and was nervous

It is to be noted that The K/Ca ratio was low, the blood sugar was slightly increased, the resistance of the skin to electric current was high, and the blister time was prolonged

CASE 69—A medical student, Jewish, aged 22, was nervous and had a tremor. He felt weak on venipuncture. He had had a duodenal ulcer since 1925. His father was nervous, with a blood pressure of 160 systolic and 170 diastolic. His mother also was nervous, and had a blood pressure of 210, with myocardial degeneration.

It is to be noted that he had a short blister time, a low K/Ca ratio, a high resistance of the skin to electric current, an increase in pulse pressure, marked flares in the reaction of the skin to the pharmacologic substances, and well marked clinical symptoms of the systemic reaction to epinephrine—pallor, headache, feeling of distress, etc.

CASE 6—A painter, Jewish, aged 49, was nervous, had vague pains and was occasionally dizzy, especially after eating. The blood pressure in November, 1926, was 160 systolic and 80 diastolic. There was a contraction in the visual fields indicating early optic atrophy (late neurosyphilis). The Wassermann reaction was positive. The roentgen examination of the chest indicated sclerosis of the aorta, and large heart. The patient died several months later from myocardial degeneration.

The low K/Ca ratio and an increase in the basal metabolic rate were the most prominent observations, there was a trace of albumin in the urine.

COMMENT

That the emotional states can alter the mineral metabolism was shown by Dresel.¹⁶ Tómasson¹⁷ also studied the correlation of mental excitation and the mineral balance. His studies, however, were made on psychopathic persons, as were the studies of Weston and Howard.¹⁸

When we review this small series of cases, the outstanding clinical complaint being nervousness (with the exception of case 2), the most striking observation in the blood seems to be an unusually low K/Ca ratio. Rather striking, too, is the relatively high resistance of the skin to electric current—in sharp contrast to the observations in the exophthalmic group.

On the other hand, these persons showed an increase in the red flare at the site of the injection of thyroxin, similar to that found in the patient with exophthalmos.

While the patient with exophthalmic goiter presented a fundamental autonomic disturbance, and seemingly a "thyroid factor" not necessarily associated with the same thyroid factor that increases the basal metabolic rate, the nervous patients presented mixed autonomic exaggerations, as well as varying reactions to epinephrine and an exaggeration of the flare due to thyroxin similar to that seen in the patients with exophthalmic goiter (and which is diminished after thyroidectomy). The differentiation of the so-called cases of "autonomic imbalance" from exophthalmic goiter has been discussed particularly by Kessel and

¹⁶ Dresel. *Klin Wchnschr* 33 311, 1924.

¹⁷ Tómasson, Helgi. *Blodets Elektrolyter*, Copenhagen, Levin & Munksgaard, 1927.

¹⁸ Weston, P. G., and Howard, M. Q. Determination of Sodium, Potassium, Calcium and Magnesium in Blood and Spinal Fluid in Manic-Depressive Insanity, *Arch Neurol & Psychiat* 8 179 (Aug) 1922.

Hyman,¹⁹ and Eason,²⁰ too, has covered the subject, so that we need not dwell on it here

We can only suggest from these limited observations that the mineral balance of the "nervous" patient is apparently altered, so that the potassium values of the serum are sometimes low. With this there appears to be an increase in the capillary permeability. That the emotional state can apparently have some influence here is made probable from the following observations:

The person examined was one of the hospital technicians, a man, aged 40, highly intelligent and normal on physical examination. He was first examined in December, 1926. At this period, his blister time was found to be six hours, and his capillary permeability 80. The pulse rate was between 68 and 72, the blood pressure was 120 systolic and 70 diastolic with a negligible effect following the injection of epinephrine hydrochloride. The basal metabolic rate was —12.

He was reexamined in June, 1927. At this time the blister time was five hours and the capillary permeability had diminished to 64, the blood pressure had diminished to 112 systolic and 70 diastolic.

We were at a complete loss to account for the high permeability of the capillaries first noted, until a subsequent history was given us by this person to the effect that during the time of the first examination he was in the process of losing his entire savings in a stock venture and was naturally under great mental strain.

CONCLUSIONS

Observations made on a small series of patients with exophthalmos reveal the following changes: shortened blister time, increased capillary permeability, lower resistance of the skin to electric current, increased serum globulins, increased serum calcium with a normal K/Ca ratio and a lower carbon dioxide combining power.

After operation, a reversal of these reactions usually occurs.

The reactivity of the skin to injections of the pharmacologic substances reveals definite changes before and after operation, involving particularly the reactions to epinephrine, morphine and thyroxin.

From an analysis of the postoperative reactions in individual cases, we believe that factors other than those responsible for the increase in the basal metabolic rate must be considered in the exophthalmic complex.

The so-called "nervous" patients of our series appear to have an associated or underlying change in the K/Ca ratio and the group has a low potassium level. In general, the capillaries of the group are more permeable, but there are individual exceptions. They resemble the patients with exophthalmos, too, in the degree of their reactivity to thyroxin. They differ markedly in having a higher resistance of the skin to electric current.

19 Kessel, L., and Hyman, H. T. *Am J M Sc* **165** 513, 1923, *Studies of Exophthalmic Goiter and Involuntary Nervous System, Diagnosis of Exophthalmic Goiter*, J. A. M. A. **88** 1478 (May 7) 1927.

20 Eason, John. *Exophthalmic Goiter*, New York, The Macmillan Company, 1927.

V PATIENTS WITH GLAUCOMA AND THEIR VASCULAR REACTIONS *

During the course of work which Goldenburg¹ carried out in connection with glaucoma, the conclusion was reached that the inherent cause lies in alterations of the capillaries of the ciliary body, these alterations consisting of an increase in permeability (probably associated with an increased metabolic activity of the cells of the ciliary body) with a resulting swelling of the body, a coincident shutting of the canal of Schlemm and an increase in the pressure of the aqueous as a result of the continued production of the fluid with diminished possibilities of its proper removal. It is our opinion that these alterations may take place rapidly and particularly in persons who are constitutionally so oriented, the capillaries of the body are more labile. That the vessels of the eye may show such sudden swelling of the endothelium has been observed by Lenaz² in a case in which the endothelial occlusion in an arterial branch was so great that an embolus was suspected.

Endothelial instability is found associated with certain endocrine or autonomic disturbances, which only in recent years have been studied more intensively. In the group showing this association are included persons with urticaria, angioneurotic edema, hay-fever, asthma, migraine and mucous colitis, conditions in all of which distinct alterations may occur in the ionic equilibrium (particularly the K/Ca ratio, CO₂ combining power, cholesterol content, etc.), alterations not yet fully explainable. To this group must be added the persons with hyperpiesis, as well as the ones with hypotension—which, according to Kylin,³ are merely different clinical responses to the same basic alteration.

During the course of the study we felt it might be of some interest to examine patients with glaucoma with particular reference to the blood chemistry, the general reactions of the skin and the vascular condition (microscopic examination of the capillaries of the skin, roentgen examination of thoracic vessels, examination of the urine, etc.)

We have examined in detail fourteen patients of the Illinois Charitable Eye and Ear Infirmary. The histories of these patients are briefly

* In collaboration with Dr. Michael Goldenburg, Illinois Charitable Eye and Ear Infirmary, and Dr. Louis Parmacek.

1 Goldenburg, Michael. *Illinois M J* 52 474, 1927.

2 Lenaz, L. *Wien klin Wchnschr* 39 1015, 1926.

3 Kylin, E. *Acta med Scandinav*, 1927, supp 19, p 1.

set forth in table 1. In making the examinations, we have carried out the routine described in part 1.⁴

When we so analyzed our small series we found that every one presented definite evidence of alteration referable to the vascular system.

Of the two patients who had syphilis, no. 145 had distinct granulations in the capillaries of the skin, albumin in the urine and, as revealed by an x-ray picture of the chest, syphilitic aortitis, no. 164 had granular casts in the urine, and the x-ray picture revealed syphilitic aortitis.

Of the three patients who had high blood pressure, no. 154 (whose blood pressure was 190 systolic and 118 diastolic) revealed an arteriosclerosis of the aorta on roentgen examination, and granulations of the capillaries of the skin. No. 170 (whose blood pressure was 188 systolic and 96 diastolic) with a blood sugar content of 320 Mg. and a basal metabolic rate of +33, had a pulse rate of 104, and the roentgen examination showed a definite sclerosis of the aorta. No. 165 (whose blood pressure was 170 systolic and 100 diastolic) had hyaline casts in the urine and a pulse rate of 110, roentgen examination showed an enlarged heart and a dilated aorta. The rest of the patients had blood pressure within the normal range. Of these, no. 150 had hyaline casts in the urine and gave roentgenologic evidence of pulmonary fibrosis, no. 153 had granular casts in the urine and gave roentgenologic evidence of arteriosclerosis, as well as of fluid in the chest. No. 137 had albumin in the urine, and the capillaries of the skin showed distinct dilatations. No. 140 had albumin in the urine and suffered from hay-fever, the roentgenogram of the chest indicated some activity at the right upper apex. No. 141 had albumin in the urine, and the capillaries of the skin showed marked granulations. No. 161 had albumin in the urine, and the capillaries of the skin showed marked dilatations. No. 148 gave a history of cerebral hemorrhage, the roentgenogram indicated a marked sclerosis of the larger thoracic vessels, and the capillaries of the skin showed marked granulation. No. 160 had asthma, in addition, the roentgenogram indicated a dilatation of the aorta, with arteriosclerosis, and with fibrosis and atelectasis of the lungs. No. 167 had low CO_2 combining power, in addition to the highest sensitivity to epinephrine observed in the group. The capillaries of the skin revealed no marked changes. The roentgen examination indicated an old pulmonary fibrosis and bronchiectasis.

4 Petersen, W. F., and Willis, D. A. Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, *Arch. Int. Med.* 38: 663 (Nov.) 1926.

TABLE 1—The Clinical Histories of Patients with Glaucoma

Case	Sex	Occupation	History of Clinical Picture	Vision	Tension Schurtz	Type	Date of Operation	Tension After Operation	Later Tension	Last Vision	Complications
117	F	Housewife	2/3/27, pain in right eye for week, headache above orbit, lacrimation and photophobia, lids normal, conjunctiva injected, iris normal, pupil contracted, cornea cloudy and stippled, anterior chamber shallow	R Had more at 18" L 20/30	R 65 L 15	Acute congestive (or inflammatory)	2/8/27 iridectomy	R 25 L 15	R 30 L 17½	As before	Reoperation necessary
110	M	Laborer	One year ago left eye was painful, but recovered without treatment, 9 months ago foreign body in left eye—although eye was not very sore, vision was bad, 3 weeks ago eye so painful patient had to stop work, eye injected, pupil dilated, cornea steamy and insensitive, hay-fever	R 20/25 L No light perception or projection	R 12½ L 45½	Acute attack superimposed on chronic congestive glaucoma	8/16/27 iridectomy				
111	F	Housewife	Trouble in left eye 3 or 4 years ago, vision gradually failed, not always painful, pain severe now and located in top of head right anterior chamber shallow, pupil dilated and not reactive to light, marked cup, left scleral staphyloma at 12 o'clock, iris drawn into staphyloma, pupil oval and not reactive to light, anterior chamber shallow, iris cloudy, fundus invisible	R 20/100 L Had more	R 36¼ L 50¼	Chronic congestive	Trephine	24			
115	M	None	Gradually failing vision for about 4 or 5 months, cataract	R 20/100 L Fingers at 3 feet	R 16 L 40	L Noncongestive (simplex)	8/2/27 iridectomy	Down to markedly improved			R Incipient cataract, central choroiditis L Cupping of disk
118	F	None	Chronic glaucoma in both eyes for several years, right operated on 3 years ago, became worse and later enucleated, left pupil dilated, cornea steamy, vitiligo, old cerebrohemorrhage	R Enucleated, had more	L 32	Chronic congestive	9/6/27 iridectomy				
150	M	Teamster	Right enucleated, left hurt 3 weeks ago with iron object, became fluid in 3 days, later cleared up, later vision became foggy, some pain, slight injection of left conjunctiva, cornea and iris normal, pupil regular, anterior chamber shallow, deep cupping of disk	R Enucleated, 20/50	L 51	Noncongestive	3/1/27 iridectomy, could not reduce iris with exercise			With glasses, 20/30	
153	M	Farmer	Vision slowly failing for past 4 or 5 years, no pain, right pupil dilated, cornea steamy, anterior chamber shallow, left pupil dilated, anterior chamber shallow, cataract	R Perception and projection poor with bright light L Very poor with bright light	R 52 L 18	Noncongestive Noncongestive	R 4/13 L 9/20 iridectomy, both eyes	11/2/27 R 13 L 52 ?			R Central opacity of lens L Larger central opacity of lens, transillumination negative

No.	Sex	Occupation	History	R	20/200	R 61	Acute congestive	10/28/27 trephine	Tension went up to 83 under physostigmin and MgSO ₄ , by proctoclysis, 11/17/27, enucleation
154	M	Laborer	Severe pain over right eye 2 weeks ago, shut 1st attack 2 years ago, vision good until 2 weeks ago, then it began to fail with pain in head, conjunctiva congested some edema in injection, cornea hazy, pupil does not react to light, anterior chamber fairly normal	R 61	R 20/200		Acute congestive	10/28/27 trephine	
160	M	Laborer	"Terrible" pain over right eye, patient unable to see, asthma		R 20/40		Acute congestive	9/12/27 deep iridectomy 10/18/27 iridectomy enlarged	9/26/27, 36
161	F	Housewife	Vision failing for past 3 or 4 years, occasional pain on right side of head, pupil widely dilated, anterior chamber shallow and lens hazy, fundus indistinct, vessels of sclera dark, tortuous, marked cup, optic atrophy, left normal, scleral vessels dilated	R 50 L 20			Chronic congestive	10/18/27 iridodiasis 12/6/27 iridodiasis	12/5/27 R 51/2 L 16 1/16/27 R 12 1/4 L 18 1/2
164	M	Insurance agent	Pain in last 4 months in right eye and side of head, pupil dilated, cornea hazy, anterior chamber deep	R 42 1/4 L Normal			Acute congestive probably secondary	9/29/27 anterior sclerotomy 11/1/27 iridodiasis	11/12/27 R 16 Wassermann reaction of blood ++++
167	F	Housewife	Vision failing for years, under care of Christian Science practitioner, right corner abraded, insensitive opacity of iris, left the same	R 16 L 12 1/4	R Light perception L Same		R Cataract L Cataract with tension congestive glaucoma	11/15/27 iridodiasis	11/22/27 Extraction of cataract, lens adherent to lens fossa, but got it interiorly with iris forceps 11/23/27, 8 30 p m, choroidal hemorrhage 11/20/27 Enucleation
165	M	Laborer	Vision failing for year, occasional pain along side of head, both pupils dilated, anterior chambers shallow, corneas stippled	R 70 L 70	R 2/200 L 1/200		Noncongestive	10/18/27 iridodiasis, both eyes	2/21/25 R 18 1/4 L 18 1/2 2/28/27 R 1/200 L Percept of light
170	F	None	Vision in left eye began failing in June, 1924, in September vision in left eye completely lost, vision in right eye began failing about the same time and was lost in April, 1927, anterior chamber fairly good, pupils dilated eccentrically, new vessels formed on iris some postsynechia, cornea hazy, arcus similarly marked, opacity of both lenses	R 80 1/4 L 85 1/2	No light perception in either eye		Noncongestive	12/13/27 iridodiasis, right eye 1/17/28 iridodiasis, left eye	2/15/28 R 40 1/2 L 13 1/2 3/15/28 R 42 L 26 Results not good

The details of the study are collected in table 2. Immediately below the averages of these details, we have tabulated the averages obtained in examinations of thirty-seven normal persons, for comparison. These thirty-seven were normal persons and persons with roentgenologic evidence of healed parenchymal tuberculosis (part 2).

In all the cases of this small series, we have established that there are definite vascular alterations, in the form of urinary changes, changes

TABLE 2—*The Results of Correlative Examinations of Fourteen Patients with Glaucoma,*

Individual Number	Blister Time, Hours	Permeability of Capillaries, %	Inflammatory Index	Calcium, Mg	Potassium, Mg	K / O Ratio	Sugar, Mg	Globulin, per Cent	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance (Electric)	Changes in Urine	Blood Pressure, Systolic	Blood Pressure, Diastolic	Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure x Pulse Rate, %	CO ₂ Combining Power
137	15	61	4	8.1	18.2	2.24	73	37		2	3.6	1.0	Trace of albumin	119	67	78	+7	+9	51.9
140	0	68	0	11.4	29.7	2.61	82	37		2½		0.45	Trace of albumin	100	70	68	+10	+10	53.6
141				9	28.2	3.13	86			2		0.2	+	118	78	84	+9	0	64.6
145	15	66	4.4	10.1	15.7	1.55	70	55	+++	2¾	+19	0.35	Trace of albumin	136	80	84	+43	+43	50.4
148	15	56	3.7	9.7	24.3	2.50	79	24		1½	+17	0.26		116	74	90	+8	+18	69.5
150	15	57	3.7	12	21.3	1.78	82	15		1½	+39	0.22	Hyaline casts	140	86	84	+6	+6	62.7
153	15	78	5	9	18.7	2.08	83	0		1½	+2	0.15	Granular casts	124	58	64	+10	+10	62.2
154	15	60	4		23.08		71	3		1½	+18	0.09	?	194	118	68			56.6
160	15	66	4.4	10.86	21.58	1.98	65	44		1½	+16	0.4	?	128	64	68	+8	+28	61.7
161	5	72	14	9.17	18.03	1.96	86	20		1¼	16	1.4	Trace of albumin	107	64	88	+25	+51	49.4
164	9	71	8	8.7	16.54	1.89	65	20	+++	2¾	-4.7	0.23	Granular casts	110	76	80	+14	+35	55.9
165	11	60	5.5	10	17.94	1.79	80	16		1½	+0.5	0.18	Hyaline casts	170	100	110			53.9
167	15	56	3.7	12	22.72	1.9	81	27		2	0.7	0.65		137	92	84	62	80	47.9
170	15	72	5	10.58	23.71	2.2	320	36			+33	0.07		188	96	104			52.5
Averages*	13.3	64	4.8	10	21.4	2.14	77	25	2+	1½	+12.4	0.48		134	80	82	+18	+29	57.2
Averages†	7	63.3	9.4	10.1	20.6	2.04	71.3	30		2	+6.3	0.35		116	69	71	+16.5	+24	58

* For 14 patients with glaucoma

† For 37 normal persons

in the capillaries of the skin, increased blood pressure, sclerosis of the larger thoracic vessels, or a history of disease known to be associated with autonomic vascular disturbances (asthma, hay-fever)

The intracutaneous reactions may also be interpreted in this direction. Thus, the flare of the reaction to morphine is diminished, and the flare of the reaction to caffeine and that of the reaction to thyroxin are absent. The wheal in the reaction to epinephrine, on the other hand, is diminished. The wheal in the reaction to thyroxin is increased.

Comparison of the Averages of These Results with the Averages for Thirty-Seven Normal Persons

Endothelial Reaction (Rumpel-Leede)	Roentgen Examination of Chest		Capillaries of the Skin (Microscopic Examination)	Reaction to Ice, Seconds	Age	Weight / Length	Cholesterol, Mg	Intracutaneous Reactions								X Ray Diagnosis
	Heart	Tuberculosis						Epinephrine, Wheal, Mm	Epinephrine, Flare, Mm	Morphine, Wheal, Mm	Morphine, Flare, Mm	Thyroxin Wheal, Mm	Thyroxin, Flare, Mm	Caffeine, Wheal, Mm	Caffeine, Flare, Mm	
+	Asthenic		Dilatation	30	61	166	222	15.1	11	13.5	10	13	0	18	0	Active tuberculosis of right upper lobe
	Asthenic	+		40	45		158	18	8	11	10.7	27	0	30	0	
	Sthenic		Granulation	15	48		267	17.4	7.7	9	7	10	13	22	0	Syphilitic aortitis
	Sthenic		Granulation	20	71	166	208	18	13.6	16	0	16	0	23	0	Arteriosclerosis (aorta)
	Asthenic	Fibrosis	Granulation	10	67	182	317	18	12	9.7	0	17	0	18	0	Pulmonary fibrosis
	Sthenic	Fibrosis		7	67	238	217	17	14	18.5	9.5	16	0	22	0	Slight arteriosclerosis, fluid in chest
	Sthenic	Healed parenchymal	Diminished dilatation	30	75	223	175	22	6.5	9.5	0	18	0	22	0	Arteriosclerosis (aorta)
	Asthenic		Granulation	20	55	181	180	23	10	13.5	0	26	0	28	0	Arteriosclerosis (aorta), bronchiectasis, emphysema
	Sthenic	Healed parenchymal, fibrosis	Normal	10	58	181	190	16	8	12	0	20	0	24	0	Syphilitic aortitis
	Sthenic		Dilatation	12	43	171	208	14	13	5.5	10.7	13	0	20	0	Hypertrophy of heart, dilatation of aorta
	Sthenic	Healed parenchymal		15	48	223	185	18	14.7	17	12.5	(Not done)				Scoliosis, bronchiectasis
	Sthenic			5	52	250	185	17	13	10	13.7	25	0	31	0	Arteriosclerosis (aorta), bronchiectasis
	Asthenic		Dilatation	5	77	158	256	17	14.25	12	9	15	0	18	0	
	Sthenic				56	247	170	(Not done)								
				15.6	58.7	199	212	17.7	11.2	12.1	6.4	18	1	23	0	
				15.5	41.8	221	228	20	9	11.3	16.2	11.4	5.8	17.4	2.38	

VI SENSITIZED PERSONS AND PERSONS WITH DISEASES OF THE SKIN

ANGIONEUROTIC EDEMA

CASE 152—A white man, American, aged 27, had a swelling of the scrotum two years prior to the examination. The swelling lasted one day and returned at intervals of from three to four months for one year. During a remission, the patient received tetanus antitoxin. Four days later, his throat and tongue were involved. Two months later, the same kind of attack occurred. The last attack had lasted six days and was disappearing at the time of the examination.

The father had had angioneurotic edema for ten years. The mother once had urticaria. Two aunts had epilepsy. The patient had suffered at various times from attacks of migraine and was sensitive to strawberries.

This patient, it is to be noted, had a short blister time, with increased capillary permeability, a distinctly vagotonic reaction to epinephrine and diminished flares of the reactions to epinephrine and morphine with increased flares of the reactions to thyroxin and caffeine.

CASE 38—A young Jewish druggist, aged 35, with a history of angioneurotic edema, had three sisters, one of whom had epilepsy, one of whom was nervous and one of whom was seemingly well. The father was 70 years of age and well. The mother was 65 years of age and suffered from neurasthenia. This patient formerly had a typical Sunday migraine. At the time of examination, he had pruritis, and was sensitive to raspberries. Formerly, ingestion of milk caused cramps and diarrhea. Watermelon still had this effect. At the time of examination, he was without angioneurotic manifestation.

As in the previous case, we find the patient in this case showing a short blister time with somewhat increased capillary permeability, but no chemical changes. The systolic reaction to epinephrine was vagotonic, but the pulse pressure showed an increase immediately after the injection. The capillaries of the skin appeared swollen and were markedly red, and in some a distinct granulation became apparent. The flares of the intracutaneous reactions (except of that to epinephrine) were all increased.

URTICARIA

CASE 171—Menstrual Urticaria. A young woman, Jewish, aged 23, a laboratory worker, was alert, nervous and rather irritable. Her family history was negative except in relation to tuberculosis. The grandfather had had tuberculosis, and the mother died of tuberculosis. The patient had malaria in 1921. At the time of the examination, she had slight mitral insufficiency. She had had a rather irregular menstrual course. The urticaria, which was generalized, began one or two days before the menstrual period, and lasted approximately a week. The patient was then free from urticaria during the intermenstrual period. The patient recently had had a curettage and since then had been free from disturbance.

The comparison of the observations during the menstrual period with the intermenstrual observations is of interest. During the menstrual period, the permeability of the capillaries was increased, the potassium level, as well as the

K/Ca ratio, was lowered, there was less cholesterol and the systolic blood pressure and the pulse rate were higher. The reaction to epinephrine was sympatheticotonic during both periods, more so during the intermenstrual time, when, too, the intracutaneous reaction to epinephrine was more marked. The wheals of the reactions to thyroxin and caffeine were larger than normal at both times.

CASE 116—A young Irish woman, aged 30, came to America four years prior to the examination. The first attack of urticaria appeared two years before the examination, when she had angioneurotic edema. Two months before, her father died of pernicious anemia and the attack in question dated from this time. The urticaria was worse at night and because of the interference with sleep the patient was rather nervous. The family history was negative. On general physical examination, the spleen was found enlarged, the icteric index was increased and bile was also present in the urine. With minor exceptions, the urticaria had persisted to the time of examination. No definite sensitization could be determined, but the skin was particularly sensitive to staphylococci. The function of the reticulo-endothelial system, as determined by administration of a vegetable oil (oleokinol), seemed practically normal.

The results of the examination were as follows. A strikingly short blister time, low permeability of the capillaries and a distinctly vagotonic reaction to epinephrine with the pulse pressure much increased. The results of all the chemical examinations were within the normal limits.

CASE 139—A stenographer, American, aged 29, had vitiligo for ten years and urticaria for some eight weeks. She had jaundice at the age of 11, for two weeks. Of late, she had been nervous, with occasional palpitation. She had a nervous breakdown at the age of 19. She felt "shaky" when she worked hard, but had suffered no loss of weight. One other sister had vitiligo and one had diabetes. The urticaria was made worse by pineapple, popcorn and watermelon.

Practically the only abnormalities were that found in the pulse rate and the vagotonic reaction to epinephrine. There was a trace of albumin in the urine. The intracutaneous reactions to epinephrine and morphine showed lessened wheals and those to thyroxin and caffeine increased wheals and flares. The patient was treated with calcium for two months. On reexamination, the blister time was somewhat shortened, the permeability of the capillaries was increased and the calcium was lower. During this time, however, the patient was somewhat improved.

ECZEMA

CASE 101—A laborer, aged 55, born in Scotland, one of our group of 100 normal men, had chronic eczema of the legs. He had a history of moderate alcoholism. The family history was negative, except that one uncle had epilepsy. The patient was rather stolid and seemingly unemotional. Fifteen years prior to the examination, he had had rather severe diarrhea and with it urticaria.

The examination of this patient revealed merely a low capillary permeability together with a diminished intracutaneous reactivity to morphine. The reaction to epinephrine was sympatheticotonic.

CASE 132—The clinical history of the patient, the most interesting of the entire group of patients, has been described. It is to be recalled that he had the lowest K/Ca ratio of all the patients, the lowest CO₂ combining power and

increased muscle reactivity The cholesterol level was high, the Kromayer light erythema faint, the pulse rate slow and the reaction to epinephrine vagotonic The wheals of the reactions to thyroxin and caffeine were somewhat increased

The results of the examination of this patient emphasize the impossibility of schematizing the results and the futility of endeavoring to place these persons in hard and fast groups The patient was typically vagotonic, but, in addition, he was suffering from a relative acidosis Despite this acidosis, the muscular irritability was high

GASTRO-INTESTINAL SENSITIZATION

CASE 54—A man, American, aged 49, showed a trace of albumin in the urine and x-ray evidence of myocarditis and sclerosis He was sensitive to peaches and strawberries (urticaria) The reaction to epinephrine (systolic) was distinctly vagotonic, but the pulse rate was sympathetotonic

CASE 172—A Greek, aged 30, who had had a positive Wassermann reaction in 1921, had Raynaud's disease The family history was negative The calcium level was high (low K/Ca ratio), the reactions to the Kromayer light and ice were faint, the blood pressure was low and the reaction to epinephrine was markedly sympathetotonic All intracutaneous reactions to the pharmacologic substances injected were marked The patient was sensitive to peaches and cherries

CASE 169—The patient had Buerger's disease (Wassermann reaction +++) He showed a high calcium level with a low K/Ca ratio The serum proteins were concentrated, the reaction to Kromayer light was faint and the reaction to epinephrine (systolic) was vagotonic The flares of all the intracutaneous reactions (except that to epinephrine) were absent The patient was sensitive to strawberries

CASE 14—A German, aged 36, an artisan, had albumin and casts in the urine, together with an undetermined reducing substance (not dextrose) He probably had gallbladder disease He was sensitive to honey and pineapple, these caused intense pain The capillaries of the skin were increased in number, and their permeability was high The calcium level was high and the K/Ca ratio was low The cholesterol level was also high and the reactions to the Kromayer light and ice were faint The reaction to epinephrine was vagotonic The wheal of the reaction to epinephrine was increased and the flare diminished

PURPURA

CASE 120—A Hungarian woman, who gave a history of sensitiveness to tomatoes, on admission had petechial hemorrhages over the body and the extremities, showers appearing at intervals of from twenty-four to forty-eight hours There was considerable blood in the urine It may be noticed that the permeability of the capillaries was high and the endothelial reaction (Rumpel-Leede) was positive The blood chemistry was normal, except for an increase in the globulins Microscopic examination revealed distinct granulations of the skin capillaries

PREVIOUS SENSITIZATION—HAY-FEVER

CASE 128—An American workman, of Irish parentage, aged 66, stated that he had had hay-fever for years In addition, he had an enlarged prostate and

x-ray evidence of arteriosclerosis of the larger vessels. The capillaries of the skin showed distinct granulations and the urine contained albumin. The blood chemistry was practically normal.

CASE 148—A white woman, aged 67, had glaucoma and vitiligo. She had had hay-fever twenty-five years prior to the examination and had had urticaria. X-ray examination of the chest showed considerable healed pulmonary tuberculosis and arteriosclerosis, and she gave a history of having had cerebral hemorrhages. The capillaries of the skin showed granulations, the reaction to epinephrine was vagotonic.

CASE 140—A white man, aged 45, suffering from alcoholism and glaucoma, had a history of hay-fever every spring. There was roentgenologic evidence of active tuberculosis. Examination of the capillaries of the skin showed dilatations, but the total number was diminished. There was a trace of albumin in the urine and the reaction to epinephrine was vagotonic.

CASE 93—An American workman, aged 53, a periodic drinker, had a history of hay-fever every fall (ragweed). In addition, he was sensitive to halibut. He was short of breath and the x-ray picture indicated a myocarditis. The reaction to epinephrine was vagotonic, the capillaries appeared to be normal.

CASE 160—A white man, American, aged 58, was suffering from glaucoma. He gave a history of asthma extending over many years. An x-ray picture of the chest indicated emphysema and bronchiectasis, together with arteriosclerosis of the larger vessels. The reaction to epinephrine was vagotonic. The capillaries appeared to be unchanged.

CASE 36—A white man, American, aged 43, had an attack of hay-fever four or five years prior to the examination. The reaction to epinephrine was vagotonic, and there was a trace of albumin in the urine.

All the members of this group showed relatively high K/Ca ratios, CO₂ combining power within normal limits and faint reactions to the Kromayer light. Their blood pressures were relatively low and their pulse rates were somewhat increased.

PREVIOUS SENSITIZATION—URTICARIA AND ANGIONEUROTIC EDEMA

CASE 45—An American workman, aged 39, had a history of scarlet fever with involvement of the kidneys at the age of 4. The blood pressure was 162 systolic and 114 diastolic. The reaction to epinephrine was vagotonic. The patient had had urticaria twenty years before.

CASE 86—A former dentist, aged 50, was extremely nervous, with a history of alcoholism. He had had angioneurotic edema twenty-five years before. The reaction to epinephrine was vagotonic.

CASE 56—An American workman, aged 44, had x-ray evidence of active pulmonary tuberculosis. He had had angioneurotic edema and dermatographia three years before. The reaction to epinephrine was vagotonic.

CASE 77—An American workman, aged 39, formerly suffered from alcoholism. His grandfather had asthma. He stated that he had had sugar in the urine and that ten years ago he had urticaria from eating sweet potatoes. The patient was

nervous He gave a vagotonic reaction to epinephrine and a positive endothelial reaction (Rumpel-Leede)

CASE 80—An American workman, aged 29, was nervous and had a distinct tremor He had had urticaria three years before He gave a distinct vagotonic reaction to epinephrine

The Results of Correlative

Diagnosis	Blister Time, Hours	Capillary Permeability, %	Inflammatory Index	Calcium, Mg	Potassium, Mg	K / Ca Ratio	Sugar, Mg	Protein, Mg	Globulin, Mg	CO ₂ Combining Power	Cholesterol, Mg	Kromayer Light Fry- them's Time, Min	Skin Resistance	Ice Retention	Basal Metabolic Rate	Blood Pressure			Reaction to Epinephrine		Weight/1 cm. th Ratio
																Systolic	Diastolic	Pulse Rate	Pulse Pressure, %	Systolic	
52 Angioneurotic edema	4	73	18	9.8	20.1	2.05	63	7.47	20	63.4	175	60	0.18	15	4.8	120	74	80	-5	Vagotonic	243
38 Angioneurotic edema	5	69	14	9.8	21	2.14	86	8.28	40	58.5		90	0.29	10	11.5	124	65	84	+31	Vagotonic	194
71 Menstrual urticaria (Intermenstrual observations)	5	73	14	12.6	17.9	1.42	72			48.7	202	75	0.08	20	8	114	66	96	+18	Sympatheticotonic	160
16 Urticaria	3½	60	17	10	19.4	1.94	78	6.98	40	46	230	(faint)	0.08		12	102	68	68	+100	Sympatheticotonic	160
39 Urticaria and vitiligo	6	65	11	9.7	18.4	1.9	81	7.10	18	50	175	120	0.20	8	5	113	71	104	+12	Vagotonic	176
01* Eczema	4¾	68.5	15	8.6	18.7	2.1	78	7.95		50	190										
	8¾	47	5.4	9.4	19.4	2.06	65	7.20	45	57.4	158	90	0.13	15	31	132	76	67	+13	Sympatheticotonic	191
32 Eczema	6	68	11.3	13.4	15	1.12	67	7.30	23	40.3	256	120	0.31	10	-1.2	132	78	56	0	Vagotonic	234
54* Sensitized	6	60	10		22		80	8.28	33	56.6		75	0.26	25	-3.4	108	68	72	+90	Vagotonic	236
72 Sensitized	12	72	6	13	21.3	1.64	76	8.16				105	0.08	45	-18	108	78	94	+90	Sympatheticotonic	166
69 Sensitized	15	62	4.1	12.3	19.24	1.53	67	9.87	20	55.1	158	120	0.23	25	-7	118	78	82	+40	Vagotonic	
14* Sensitized	7	74	10.5	11.2	19.6	1.75	67	8.06	37	65	278	95	0.20	40	2.7	128	80	76	0	Vagotonic	193
20 Purpura	6	82	13	10	19.9	1.99	71	7.95	50	52.2	185	70		14	-5						172
28* Hay-fever for years	15	68	3.8	10.2	19.7	1.93	79	8.06	55	58.1	230	240	1	24	-18	122	70	84	+24	Vagotonic	180
48 Glaucoma	15	56	3.7	9.7	24.3	2.5	79	7.97	24	69.5	317	85	0.26	10	+17	114	72	94	+18	Vagotonic	182
40 Glaucoma	15	68	4.05	11.4	29.7	2.61	82	6.25	37.5	55.6	158	150	0.45	40		100	70	70	+10	Vagotonic	
93*	6	50	8.3	7.6	24.5	3.22	70	8.59	42	57	230	90	0.25	12	0	113	71	86	+19	Vagotonic	267
60 Glaucoma	15	66	4.4	10.86	21.53	1.93	65	8.16	44	62.7	190	70	0.4	10	+16	128	64	68	-28	Vagotonic	190
36* Cardiovascular renal disease	8	58	7.2	12.1	26.3	2.17	90	8.28	33	57.6		120	0.11	20	+1.3	104	50	84	+28	Vagotonic	227
45* Cardiovascular renal disease	6	54	9	11.2	16.6	1.48	77	7.73	40	54.3		45	0.28	20	+20	102	114	84	+8	Vagotonic	317
86* Nervous	15	58	3.8	12.6	15.9	1.26	94	6.33	40	55	185	105	0.36	25	+6.4	118	60	74	-14	Vagotonic	176
56* (Roentgen evidence) tuberculosis	6	61	10	9.8	28.6	2.52	65	9.36	35	56.6		135	0.32	15	-17.9	124	88	80	+22	Vagotonic	247
77* Nervous	9	87	10	10.8	15.6	1.44	71	6.98	36	60.6	196	240	1	35	+7.9	126	78	82	+7	Vagotonic	187
80* Nervous	6	91	15.1	8	13.7	1.7	69	8.28	33	53.2	222	100	1.6	30	+13	116	68	64	+12	Vagotonic	212

* The patient belonged to the group of 100 so called "normal" men

COMMENT

When considering the results of the examination of the group of persons who were presumably sensitized, it must be kept in mind that one can hardly expect distinct chemical alterations in conditions in which the clinical manifestations were so frequently evanescent and transitory,

Nathan and Stein¹ rightly emphasized that a single determination of the K/Ca ratio—for instance, during the course of a dermatosis—hardly gives a true picture, typical for the disease. One must make repeated determinations in order to obtain a true insight into the fluctua-

Examinations of Sensitized Persons

Changes in Capillaries	Arteriosclerosis, X-Ray	Healed Tuberculosis	Active Tuberculosis	Changes in Urine	Intracutaneous Reactions								Endothelial Reaction	Age	Sex	Associated Conditions and History						
					Epinephrine		Morphine		Thyroxin		Caffein											
					Wheal, Mm	Flare, Mm	Wheal, Mm	Flare, Mm	Wheal, Mm	Flare, Mm	Wheal, Mm	Flare, Mm										
				Hyaline casts	26	75	95	10	9	8	9	10		27	M							
Dilatations, granulations					18	86	88	25	10	2	4	8	11	39	M							
Dilatations	+			Albumin, faint trace	17	5	12	5	0	18	0	20	0	23	F							
Dilatations	+				26	65	10	12	2	20	0	17	8	23	F							
				Bile	20	4	7	1	9	2	8	5	0	20	F							
Dilatations				Albumin, faint trace	16	11	9	5	7	5	14	12	5	29	F							
Dilatations	+				19	6	7	10	2	6	10	0	18	1	0	55 M						
Dilatations	+				18	4	9	1	11	6	17	6	13	4	5	22, 6	26 M					
				Albumin, trace	21	2	10	4	11	18	12	0	11	0	49	M	Sensitization to peaches and strawberries					
Dilatations	+				22	1	16	17	5	8	5	18	16	20	7	5	30 M	Raynaud's disease, syphilis, 1921, sensitization to peaches and cherries				
Retina pale	+				20	8	11	13	0	18	0	21	0	27	M		Buerger's disease, syphilis (Wassermann)					
				Casts	24	4	6	2	13	2	7	2	15	5	9	8	10	36 M	sensitization to strawberries			
Granulations				Blood	21	2	7	2	9	6	8	2	12	1	0	13	0	18 F	Probably gallbladder disease, intense			
Granulations	+	+		Albumin				12	6	10	2	14	4	0	22	6	0	—	66 M	caused by honey and pineapple		
Granulations	+				18	12	8	7	5	0	17	0	18	0	—	67	F		Purpura hemorrhagica, sensitization to			
Dilatations			+	Albumin	18	8	11	10	7	27	0	30	0	—	45	M			matoes			
					20	4	8	6	12	1	15	10	0	22	4	0	—	52	M	Hay-fever for years		
	+	+			16	8	11	0	20	0	24	0	—	58	M				Hay-fever 35 years ago, cerebral hemorrhage			
				Albumin	20	8	14	2	11	2	18	7	4	0	—	43	M			urticaria		
					20	4	9	8	14	2	21	4	16	4	12	20	4	8	—	39 M	Hay fever every spring, alcoholism	
					18	8	11	10	6	15	4	12	4	22	2	0	—	50	M	Hay-fever every fall, sensitization to halibut		
		+			17	2	5	8	10	8	22	4	13	4	7	21	4	7	—	44 M	myocarditis, formerly dipsomania	
					14	10	8	12	6	25	10	15	4	17	12	4	—	39	M	Asthma, emphysema		
Granulations					14	8	12	4	12	1	19	2	13	4	9	2	16	2	7	—	29 M	Slight attack of hay-fever 45 years ago
																						Scarlet fever with kidney involvement and
																						urticaria 20 years ago
																						Angioneurotic edema when a dental student
																						20 years ago, alcoholism
																						Angioneurotic edema 3 years ago, dermatographia
																						Grandfather had asthma, drug addict
																						urticaria 10 years ago, sensitization to
																						sweet potatoes
																						Sugar in urine formerly, alcoholism, urticaria in 1922
																						tremor

tions that are constantly taking place. We have emphasized this point of view in our study of the lymph changes during shock, etc.²

¹ Nathan, E., and Stern, F. *Klin Wchnschr* **7** 1375, 1928

² Petersen, W. F., Milles, Geo., and Muller, E. F. *Ztschr f Exper Path und Therap* **60** 336, 1928, Petersen, W. F., Muller, E. F., and Boikan, W. *J Inf Dis* **41** 405, 1927

The angioneurotic edemas and the urticarias studied seemed to be characterized by a short blister time and a relatively high inflammatory index. During an attack, the K/Ca ratio appeared to be lower. In general, the sugar level was higher. The menstrual urticaria was associated with a relative acidosis, and the reaction to epinephrine, in contradistinction to the reaction in other cases, was sympathicotonic. Changes in the capillaries of the skin and changes in the urine were, of course, commonly associated. The intracutaneous reactions to the pharmacologic substances injected were not characteristic.

The small group of persons with gastro-intestinal sensitization all had high calcium levels and low K/Ca ratios. In two, however, distinct vascular diseases (Raynaud's and Buerger's) were associated.

Of the six persons with a history of hay-fever, three had glaucoma. Here the blood chemistry was changed so far as the K/Ca ratio was high. All were distinctly vagotonic and the capillary permeability was low in each case.

On the other hand, the persons with a history of previous angioneurotic edema and urticaria seemed to be of a somewhat different type. They were distinctly nervous and had low K/Ca ratios, but were, nevertheless, distinctly vagotonic. With two exceptions, both highly nervous persons, all showed low permeability. These two patients (nos 77 and 80) had high resistance of the skin to electric current, high permeability of the capillaries and lessened thyroxin wheals.

The endothelial reaction of Rumpel-Leede did not seem to be characteristic for the groups.

VII A STUDY OF EIGHTY-THREE TUBERCULOUS PATIENTS

A GENERAL CORRELATIONS

The study of resistance to tuberculous infection, conditioned by innumerable biologic interactions, seemingly offers insurmountable difficulties. The cellular factors, the still intangible effect of sensitization, intercellular and intracellular digestion, humoral and fixed antibodies, endocrine, vitamin, and chemical equilibriums must be considered. Add to these chance pathologic complications, constitutional inequalities, peripheral and visceral autonomic vascular and metabolic responses and emotional factors, as well as environmental influences, and one begins to shuffle some of the cards of the intricate game—all this, of course, without considering differences in the virus itself.

The organism has but two means at its disposal in overcoming the clinical disease—resorption, i.e., digestion, and its antithesis, encapsulation or insulation. Early in the disease, the former method is probably frequently successful, even in well advanced diseases. It probably plays a rôle of greater importance than is usually believed, especially in peripheral tuberculosis. But from the practical clinical standpoint it appears that the inhibition of digestion, the suppression of inflammatory response is of greater importance for the welfare of the patient with pulmonary tuberculosis.

Hippocratic medicine was clearly cognizant of the seasonal influence on the mortality from tuberculosis. General biologic activation in the spring, incident to environmental and intrinsic changes, is followed by dissemination of the virus. It is a condition that cannot be explained on any anatomicopathologic basis. Not only is the virus disseminated, the endothelium and other tissues of the body are receptive. This factor, as well as the analogous effect of the menstrual cycle, we discussed previously at some length¹. Here, too, we pointed out the possible significance of changes in the status of the capillary endothelium.

In the analysis of the results of the examinations of the group of 100 so-called "normal" men (part II), we pointed out that nine gave roentgenologic evidence of active parenchymal lesions. The persons examined were workingmen, in the majority, the lesions did not present sufficient clinical manifestations to make the men aware of an unusual pulmonary disturbance. In the analysis, however, we found that this group did show a number of deviations from the "normal" (prolonged

1 Levinson, S. A., and Petersen, W. F. *Am Rev Tuberc* **15** 681 1927

TABLE 1—Index of the Tuberculous Patients Examined

Patient	Age	Nationality	Advance Diagnosis,* Pulse Tem- Rate perature	Result of Roentgen Exami- nation for Tuber- culosis	Dura- tion of Activ- ity, Weeks	Condi- tion on Exami- nation, Weight †	Condition at Time of Writing ‡	Outcome
1	27	Jewish	M A A 72-78 98 2 98 4	Positive, not active	156	M A A →	M A A G →	Discharged, living, improved
2	22	Jewish	Min B 60-76 97 98 4	Re apical healed pa- renchymal	20	Min B →	Min B G →	Discharged, living, condition quiescent
3	21	Polish	Min A 72 96 98 2 98 6	Negative	6	Min →	Min A G → colloid goiter	Sanitarium
4	30	American	Min A 68-72 97 98 2	Negative	208	Min →	Min A G →	Discharged, living, improved
5	20	Swedish	M A B 104 120 98 98 8	M A *	60	M A B ↑	M A B F →	Sanitarium
6	27	German- American	Min A 66-84 97 99 4	Apical	260	Min A ↑	Min A G ↑	Sanitarium
7	54	Norwegian	F A B 72 94 96 8 90 2	F A *	23	M A B ↓	F A B P ↓ tuberculosis of larynx	Discharged, died
8	35	Mexican	Min A 70-90 97 98 6	Negative	26	Min A ↑	Min A G ↑	Discharged, living, condition arrested
9	43	Polish	M A A 80 92 97 2 99	F A	94	M A A →	M A A P, → dry pleurisy and arthritis	Died
10	27	American	Min A 80-92 98 98 2	Negative	350	Min A →	Min A G →	Discharged, living, improved
11	42	American	Min A 72 80 97 6 98 6	Negative	22	Min A →	Min A G →	Discharged, living, improved
12	37	German	M A A 84 88 97 8 99 4	F A	208	M A A →	F A A P → cyst adenoma of thyroid, tuber- culous colitis	Died, April, 1929
13	23	American	Min B 70 82 97 98 4	Negative	23	Min B →	Min B G →	Discharged, living, improved
14	17	American	Min B 72-84 97 8 98 6	Tubereu- losis of hilum	16	Min B ↑	Min B G ↑	Discharged, living, improved
15	40	Norwegian	F A A 80 92 96 98 6	F A	260	F A A →	F A A P → tuberculous laryngitis and enteritis	Discharged, living, not improved
16	25	Polish	Min A 78-80 97 98	Tubereu- losis of hilum	572	Min A ↑	Min A G ↑ tuberculous colitis	Discharged, living, condition arrested
17	40	German	Min A 76 80 97 8 98 6	Negative	17	Min A →	Min A G →	Discharged, living, condition quiescent
18	36	Swedish	F A B 100-115 97 102 4	Positive	260	F A A ↓	F A A P ↓ Wassermann 4 plus, cavities in lung, artificial pneumothorax, spon- taneous hemorrhages from lung	Died
19	54	Irish	F A B 84 88 97 4 98 6	Positive	260	F A A →	F A A G → Wassermann 3 plus, syphilitic aortitis	Sanitarium
21	32	Norwegian American	Min A 78-100 97 98 8	Positive	28	Min A ↑	Min A G ↑	Discharged, living, condition quiescent

* In diagnosis of tuberculosis, M A means moderate advanced at time of examination Min, minimal or ineipient, and F A, far advanced, A, B and C added to these designations denote degrees of activity

† → means weight stationary at time of examination, ↑, weight increasing, ↓, weight decreasing

‡ In this column, G means good prognosis at time of examination, F, fair prognosis, and P, poor prognosis

TABLE 1—Index of the Tuberculous Patients Examined—Continued

Patient	Age	Nationality	Advance Diagnosis, Pulse Tem- perature	Result of Roentgen Exami- nation for Tuber- culosis	Dura- tion of Activ- ity, Weeks	Condi- tion on Exami- nation, Weight	Condition at Time of Writing	Outcome
22	41	Dutch	M 1 1 80-90 95 6-9 S 8	T 1	130	M A A ↓	T A A G → fibroid	Sanitarium
23	22	Polish	F A A 71 80 98 6 9 S 6	Positive	101	T A A →	F A A F →	Sanitarium
24	37	Austrian	M A A 76-81 97 9 S	Positive	30	M A B ↑	Min A G →	Discharged, living, improved
25	25	Polish	T A A 86-88 97 9 S	Positive	111	T A A ↓	T A C P ↓	Died
							Spontaneous collapse	
26	21	American	M 1 A 72-80 95 9 S 6	Positive (cavity in right apex)	156	M A B →	F A A P →	Died, March, 1920
							Tuberculous enteritis	
27	43	German American	M 1 A 78 90 95 4 9 S 6	T 1	101	M A A ↑	M A A G ↑ fibroid	Sanitarium
28	42	Bohemian	T 1 B 72 102 97 8-101 3	T 1	312	I A A →	F A C P ↓ tuberculous enteritis and meningitis	Died
29	31	American	Min 1 72-90 98 9 S 6	Positive	213	Min A →	Min A G →	Discharged, living, condition arrested
30	20	Italian	M A 1 94 100 97 9 9	Positive	104	M A A →	M A A G →	Discharged, living, condition quiescent
31	21	Austrian	Min B 68-72	Positive	230	Min B →	M A A F →	Sanitarium
32	27	Irish	T A A 72 86 97 9 S 6	In apex	26	F A A →	F A A F →	Discharged, living, condition arrested
33	29	Finnish	M A B 90 100 95 2 9 S 6	T 1	780	M A B ↓	M A B G →	Discharged living, condition quiescent
34	25	American	T A B 72 88 97 4 9 S 8	T A	101	F A B →	F A B P ↓ Wassermann 4+, dermatitis exfolia- tiva, cavities in lungs	Discharged, died
35	40	Polish	Min B 70 90 97 4 9 S 6	Negative	29	Min B →	Min B G →	Discharged, living, condition quiescent
36	42	Polish	T A A 80-98 94-100 4	T A	312	F A A ↓	F A A F ↓	Died, November, 1928
37	17	Jewish	Min A 80 81 97 2 9 S	Negative	823	M A →	Min A G →	Discharged, living, condition quiescent
38	42	Norwegian	T A B 74-92 98 9 S 6	F A	276	F A B →	F A A F →	Discharged, living, condition arrested
39	45	American	M A B 72 90 97 9 S 6	F A	156	M A B ↑	M A B F ↑	Sanitarium
40	26	Bohemian	F A B 74-93 97 8 9 S 6	M A	260	F A B →	F A B F →	Discharged, living, condition quiescent
41	20	Jewish	F A B 78-100 97 4 9 S 8	F A	78	F A B →	F A B F →	Discharged, living, improved
42	29	German	F A B 78-84 97 2 9 S 4	F A	156	F A B →	F A B P → tuberculous laryngitis	Sanitarium
43	20	American	M A B 80 86 97 9 S 6	Positive, fluid	52	F A A ↑	M A A G ↑ pleurisy, fluid	Sanitarium
44	31	Swedish	M A A 74 106 98 9 9 S	Positive, fluid	44	F A A ↑	F A A F ↑ fluid	Discharged, living, condition arrested

TABLE 1—Index of the Tuberculous Patients Examined—Continued

Patient	Age	Nationality	Advance Diagnosis, Pulse Rate	Tem- perature	Result of Roentgen Exami- nation for Tuber- culosis	Dura- tion of Activ- ity, Weeks	Condi- tion on Exami- nation Weight	Condition at Time of Writing	Outcome
45	34	American	F A 86 110	B 97 100	F A	104	F A A ↑	F A A F ↑	Discharged, died
46	24	German	F A 92 100	B 98 4 98 8	F A	130	F A B ↑	F A A G ↑	Sanitarium, improved
47	21	Polish	F A 100 120	B 98 8 100 4	F A	156	F A A →	F A A P ↓	Died
48	21	Lithuanian	F A 80 88	A 98 4 98 6	F A	270	F A B ↓	F A C P ↓	Died
								cavities in lungs tuberculous laryn- gitis and enteritis	
49	38	German	M A 72 98	B 98 2 100	F A	70	M A B ↑	M A B P →	Discharged, died
								tuberculous enteritis	
50	21	Polish	Min 76- 80	B 97 2 98 6	Positive	70	Min ↑	M A A G →	Sanitarium
51	30	Danish	M A 80 92	B 97 4 98 8	F A	64	M A B ↓	F A B F ↑	Sanitarium stationary
								pneumothorax, thoracoplasty	
52	19	American	F A 76 104	B 98 4 99 8	Positive fluid	52	F A B ↑	M A A F ↑	Discharged, living, improved
								serofibrinous pleuritis, tuber- culous enteritis	
53	20	German	M A 86 120	B 97 4 99 8	Positive	38	M A B →	M A B P ↓	Discharged, living, not improved
54	20	German	M A 76- 94	B 97 99	Positive	101	M A B ↑	M A A F ↑	Discharged, living, improved
55	21	Swedish	M A 68- 88	A 97 6 98 6	Positive, fluid	104	M A B ↑	M A B F ↑ fluid	Sanitarium
56	26	Swedish	M A 78 88	A 98 -98 6	Positive	208	M A A ↑	F A A F →	Sanitarium
57	22	Irish	M A 62- 82	A 97 98 2	M A	208	M A ↑	M A G ↑	Discharged, living, improved
								pleurisy, arthritis	
58	28	American	F A 80 100	B 97 -100 8	Positive	208	F A B ↑	F A B P →	Sanitarium
59	20	Austrian	F A 80- 90	B 98 2 98 8	Positive	156	F A B →	F A B P →	Sanitarium, fair condition
								pleurisy	
60	26	Swedish Norwegian	M A 88 96	A 97 -98 6	F A	108	F A C ↓	F A C P ↓	Died
								cavities in lung, enteritis, colitis	
61	25	American	F A 84- 96	C 98 99 8	F A, emphysema	260	F A C ↓	F A C P ↓	Discharged, died
								artificial pneumo- thorax, renal tuberculosis	
62	49	Irish	F A 70 84	A 97 6-98 8	Old tuber- culosis, fluid	312	F A A →	F A A F →	Sanitarium, well
								old tuberculosis with fluid, artifi- cial pneumo- thorax in 1926	
63	25	Bohemian	F A 90 100	A 98 -98 6	F A	104	F A C ↑	F A C P ↓	Sanitarium
								phrenicotomy, thoracoplasty	
64	31	Swedish- English	F A 80 84	B 97 6 98 6	F A	101	F A B ↑	F A B P ↓	Died, March, 1929
								multiple cavities in lung	

TABLE 1—Index of the Tuberculous Patients Examined—Continued

Patient	Age	Nationality	Advance Diagnosis, Pulse Rate	Tem- perature	Result of Roentgen Examination for Tubercu- losis	Dura- tion of Acti- vity, Weeks	Condi- tion on Exami- nation, Weight	Condition at Time of Writing	Outcome
65	52	German	M 1 B 92 98	97 97.5	Old tuber- culosis	31	M 1 A →	M 1 A G →	Discharged, living, condition quiescent
66	45	Swedish	F 1 B 88-108	96 100	F 1	150	F 1 B ↓	F 1 C P ↓	Died
67	23	Swedish	F 1 B 78 102	98 98.6-100.6	F 1	60	F 1 B ↑	F 1 C P ↓	Sanitarium, active
68	20	American	M 1 A 92 138	98 98.6 103.4	F 1	64	M 1 A ↑	F 1 B P ↓	Died
69	34	German	F 1 B 80 100	98 98.4 102	F 1	208	F 1 B ↑	F 1 C P → tuberculous laryngitis	Died
70	45	Polish	F 1 B 82 90	98 98.4 99	F 1	468	F 1 B →	F 1 B F → dry pleurisy	Died, December, 1928
71	41	American	M 1 B 80-82	98 98.4	F 1	156	M 1 B ↑	F 1 A F ↑	Sanitarium
72	26	Irish	Min B 72 88	97 99	Of hilum	89	Min B ↑	Min B G ↑	Discharged, living, condition arrested
73	43	American	M 1 B 94-88	97 98-99	F 1	26	M 1 B ↑	M 1 A F ↑ diabetes	Discharged, living, improved
74	45	Swedish	M 1 A 88 108	97 98 98.6	F 1	156	F 1 B ↓	F 1 B P ↓ diabetes	Died
75	33	American	M 1 B 92-116	97 98 100.2	F 1	55	F 1 A →	F 1 A F →	Died, living, im- proved
76	38	American	F 1 B 92 122	98 98.4 100.4	F 1	52	F 1 B ↑	F 1 A F ↑	Died, living, con- dition quiescent
77	41	American	M 1 B 67 94	96 96 98.8	Positive	180	F 1 B →	F 1 B F →	Died
78	27	Japanese	M 1 B 88 120	98 98.8	Positive fluid	40	M 1 B ↓	F 1 B P ↓ serofibrinous pleuritis	Discharged, died
79	17	American	M 1 A 76-92	97 98 98.9	M 1	100	M 1 A ↑	M 1 A F ↑	Sanitarium
80	35	American	Min B 68-86	97 98 98.2	Old tuber- culosis	52	Min B ↑	M 1 A G ↑	Discharged, living, condition arrested
81	25	American	F 1 B 78 84	97 97.4 99	Positive	156	F 1 A ↓	F 1 A F ↓	Discharged, liv- ing, improved(?)
82	37	German	M 1 B 80 90	97 98 98.6	Positive	156	F 1 A ↑	M 1 A G ↑	Sanitarium, condition quiescent
83	39	Slavic	M 1 B 80 92	97 98 99.8	F 1	130	F 1 B ↑	F 1 B P ↓	Died

blister time, decreased permeability, lowered inflammatory index, abnormal K/Ca ratio, increased globulin, increased basal metabolic rate, diminished resistance of the skin to electric current, increased muscular irritability, increased pulse rate and blood pressure, delayed reaction to ice, etc.) The members of the group were considerably older than the average and some of the changes must be ascribed to age.

Nevertheless, we deal here with a tuberculous group apparently having a chronic form of the disease with little constitutional disturbance. We must assume that these persons are relatively resistant. Certain definite deviations (chemical, vascular, nervous, etc.) appear to be associated with this status.

One of the factors is a reduction of the inflammatory response. This diminishes, in general, with progressing age, but seems accentuated in the tuberculous group. For fifty persons with an average age of 58, the inflammatory index averages 8. Our group of nine with an average age

TABLE 2—*A Summary of the Results of the Examinations of*

Clinical Classification of Tuberculosis	Cases	Sputum, per Cent Positive	Wassermann Reaction, per Cent Positive	Tuberculin Fixation, per Cent Positive	Daranyi Reaction, per Cent Positive	Capillary Permeability Ratio	Blister Time, Hours	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Sugar, Mg per 100 Cc	CO ₂ Combining Power	Cholesterol, Mg per 100 Cc	Lecithin, Mg per 100 Cc
Incipient A	12	0	0	16	25	63	8.6	7.6	9.1	20.8	2.27	80	53.2	186	18
Incipient B	7	0	0	0	43	69	7	10	10.7	18.5	1.73	77	56.4	199	17.4
Moderately active A	13	30	0	46	61	70	8.4	8.8	10.8	17.1	1.6	86	58.7	211	16.5
Moderately active B	12	50	0	58	83	67	7.4	10.4	10.2	19.6	1.92	86	59.3	192	15.6
Far advanced A	16	69	6	87	81	70	7.2	9.9	9.8	19	1.93	83	54.5	186	15.9
Far advanced B	18	83	11	72	72	62	6.4	9.6	10.5	19.8	1.87	83	55.1	207	15.3
Far advanced C	5	80	0	60	100	77	11.2	6.8	10.5	18.4	1.75	89	50	192	16.9

TABLE 3—*A Comparative Summary of the Results of the Examinations of Tuberculous*

Type of Patients in Group	Cases in Group	Blister Time, Hours	Capillary Permeability, per Cent	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Sugar, Mg per 100 Cc	Globulin, per Cent	Serum Protein, per Cent	Kromayer Light Erythema Time, Min	Basal Metabolic Rate,	Resistance of Skin to Electric Current, Megohms per Sq Cm	Muscle Reaction, M ₂	Blood Pressure		Pulse Rate
Group of 100 "Normal" Men																	
Actually normal	20	6.7	63	9.4	10.2	20.6	2.05	71	33	8.04	130	+7.5	0.37	3.2	115	68	66
Showing healed parenchymal tuberculosis	12	7.3	65	9	10.3	20.3	1.97	73	24	7.68	120	+7	0.32	3.6	115	68	76
Showing active parenchymal tuberculosis, roentgenologically	9	8.4	59	7	9.6	20.1	2.08	70	41.7	8.08	114	+18.2	0.28	2.2	133	73	78
Group of Patients in Sanatorium																	
Gaining weight	36	7.2	65.3	9.5	10.6	18.9	1.80	85	33	8.75	90	+7.4			121	73	89
Stationary	32	7.6	66.2	8.6	10.4	20.1	1.96	84.7	27	8.55	91	+8			121	70	88
Losing weight	13	7.7	69.6	9.7	10.2	17.7	1.73	86.6	43	9.03	79	+8.4			112	72	91

of 58.7 has an index of 7.5. The slowing of the reaction to ice is in line with the expectancy from the age of the group (column 19, table 1, part I).

The diminution of the inflammatory response has taken place despite an increase in the basal metabolic rate, and the weight length ratio gives evidence that no serious inroad has been made so far as the general well being of the group is concerned.

Apart from the definite increase in the basal metabolic rate, the increase in globulins, the definite disturbance of the K/Ca ratio, the increase in the pulse rate, etc., offer evidence of the activity of the disease

Tuberculous Persons Correlated on the Basis of Clinical Classifications

Corpuscles/Plasma Ratio	Kromayer Light Dry-thema Time, Min	Complexion	Endothelial Reaction, per Cent Positive		Reaction to Ice, Seconds	Ophthalmics, per Cent Pathologic	Basal Metabolic Rate	Urine, per Cent Pathologic		Influenza, per Cent Positive	Leukocyte Count	Pulse Rate	Blood Pressure		NaCl Test (McClure-Aldrich), Min	Reaction to Tuberculin, Mm		
													Systolic	Diastolic		24 Hours	48 Hours	72 Hours
43 00/57	84	5	41	13	0	+1.7	0	66	9,700	83	121	71	72	6	67	32		
38 00/62	100	5	28	16	0	+0.8	14	43	11,800	77	109	65	70	78	9	5		
41 60/58.4	94	1.4	38	10.4	0	+0.2	0	38	11,900	86	120	72	75	7.4	4.1	2.4		
39 25/60.75	100	1.5	33	13	0	+3.4	0	50	13,008	89	117	72	78	9	4	1.6		
40 00/60	90	4.3	44	11.5	6	+7.4	31	44	13,000	89	119	70	85	8	8	5		
36 30/63.7	83	4.2	39	10.3	5	+1.4	22	41	13,300	97	118	70	75	8.4	7	4.5		
39 30/60.7	97	2.8	40	11.8	20	+1.5	40	20	10,500	104	113	75	93	8.6	9	4.8		

Persons and of "Normal" Persons on the Basis of the Weight Curves

Pulse Pressure, per Cent	Reaction to Epi-nephrine	CO ₂ Combining Power	Reaction to Ice, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg per 100 Cc	Lecithin, Mg per 100 Cc	Sputum, per Cent Positive	Tuberculosis Fixation, per Cent Positive	Daranyi Reaction, per Cent Positive	Endothelial Reaction, per Cent Positive	Leukocyte Count	Increase in Leukocyte Count after Intracutaneous Injection of Aolin, per Cent	Corpuscles/Plasma Ratio	Tuberculin Reaction, Mm			NaCl Test (McClure-Aldrich), Min
															24 Hours	48 Hours	72 Hours	
15	21.6	56	14.7	38.3	229	211												
21	26	57.1	16.8	42	221	226												
11	23	58.8	21	58.7	215	208												
-5	-5	57.5	12	28.6	195	199	16.3	43	60	73	43	10,680	5	38.2/61.8	8	7	4.7	85
-4	-0	55.3	12	32.7	197	200	16.7	46	46	60	37	12,900	4	40.8/59.2	8.1	7.1	3.4	77
-5	-5	55.8	10	33.2	180	193.3	15.4	77	61	70	30	11,400	1	40.5/59.5	7	4.8	2	62

In order to investigate further some of the interrelations of the resistance and the chemical status of these persons, we made a study of eighty-three patients of the Municipal Tuberculosis Sanitarium. The patients (all men) in various stages of clinical activity and progression were selected so as to give us a fair cross-section. In table 1 are recorded the serial number of each patient, his age, his clinical status, the x-ray diagnosis and the complications.

ANALYSIS ON THE BASIS OF THE CLINICAL CLASSIFICATION

In table 2, we present summaries of the results of the examinations of the patients with tuberculosis when arranged on the basis of clinical classifications. It is unnecessary to point out that an analysis on such a basis affords little insight into any actual correlation between resistance and the chemical and autonomic status of the patient. A case of far advanced tuberculosis may be one that is chronic, and associated with

TABLE 4—Results of Examinations of Patients Who Were in Good

Patient	Diagnosis	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Estimation Time, Min	Reaction to Ice, Seconds	CO ₂ Combining Power
55	M A B	6.5	82	12.6	12.9	21.5	1.66	40	10.7	100	10	61.2
16	Min A	13	69	5.3				26	8.16	60	12	31.4
6	Min A	6	56.1	9.3	9.4	14.2	1.5	17	8.77	20	12	36.8
21	Min A	7	64.1	9.5	8.8	19.4	2.2	30	6.98	110	16	58.5
80	Min B	6.5	64	9.8	9.97	19	1.9	12	7.91		12	31.8
79	M A A	9	67.2	7.4	11.5	17.5	1.5	20	8.94		18	55.5
39	M A B	10.5	69.4	6.1	9.3	16.3	1.75	26	7.73	175	10	56.9
27	M A A	9	51.9	5.7	13.1	15.2	1.16	22	9.64	140	7	58
43	F A A	6	69.2	11.5				3	6.71	60	5	56.8
46	F A B	6	72.8	12.1	9.9	22.5	2.27	42	9.85	90	12	55
44	F A A	7	80.9	11.5				32	7.41	78	5	48.4
45*	F A A	7	65.1	8.6	11.8	20.6	1.74	40	9.45	100	20	56.9
76	F A B	6.5	70.9	10.9	12.5	19.45	1.55	65	9.87		15	60.9
82	F A A	8	61.3	7.6	9.4	17.7	1.87	25	12		12	49.4
52	F A B	6	57	9.5	9.6	19.3	2.1	100	11.5	75	2	
71	M A B	6	75.9	12.6	12.2	19.1	1.57	38	7.63		17	64
16	Averages	7.5	67.3	9.37	10.7	18.5	1.75	33	8.92	91.6	11.5	56.1

* Died, 1929

relatively high resistance, a case of minimal manifestation of the disease, one that may go on to death in a relatively short time.

When we examine these averages, we find no consistency. While the permeability of the capillaries of the skin ranges from 63 in the patients with the minimal manifestations to 77 in the patients with the far advanced conditions, the intermediary groups show no progressive relation. In general, calcium increases, but here, too, there is no consistent progression. Potassium diminishes, as do lecithin and the CO₂ combining power, but all the averages are irregular. As is to be expected, the Darányi reaction, the globulins, the complement fixation and the basal metabolic rate increase in fairly consistent fashion.

ANALYSIS ON THE BASIS OF THE WEIGHT CURVE

The analysis based on the weight curve of the patient might offer a better approach and in table 3 we present such a summary. Two patients of the series are not included because of the briefness of the period of observation at the sanitarium. For purposes of comparison, we present first the averages for the truly normal persons, those showing roentgen evidence of "healed" tuberculosis and those showing roentgen evidence of "active" tuberculosis of our series of 100 "normal" men.

Condition When Examined and Who Improved During the Two Years Following

Vascular Reaction to Epinephrine	Epinephrine, Wheal Diameter, Mm	Epinephrine, Flare, Radius, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Cholesterol/Leucithin	NaCl Test (McClure- Aldrich), Min	Reaction to Tuberculin, Min			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
Vagotonic	18	14	7	8	16	85	17	5	5	—	38.2
Sympatheticotonic	15	21	3	0	112	80	0	0	0	—	36.3
Vagotonic	15	6.7	10	7.5	102	80	8	10	0	—	40.5
Vagotonic	17	8.7	4	0.5	0.94	77	1	1	4	—	42.8
Sympatheticotonic	18.7	7.8	10	2.5	1.32	60	12	12	12	—	34.2
Sympatheticotonic	12.2	6.3	10	2.5	1.77	70	5	4	4	++++	32.4
Vagotonic	13.5	7.6	10	2	1.53	95	20	6	0	A C ?	38.4
Vagotonic	15.2	2.8	8	1.5	1.38	77	8	6	0	++	52.05
Vagotonic	14.5	11.7	6	2	1.38	120	12	25	25	+	35.7
Vagotonic	18	12.6	10	0	1.3	60	5	10	14	++	26.8
Vagotonic	16.2	8.7	12	0	1.51	105	8	15	14	++	45
Vagotonic	16.5	9.7	10	10	1.41	62	9	11	13	++++	32.9
Sympatheticotonic	10	11.6	10	0		75	8	8	8	++	35.4
Vagotonic	16	4.7	12	0	1.15	120	8	6	4	+	34.6
Vagotonic	13.7	17	10	10	1.5	115	10	3	3	+++	46.5
Sympatheticotonic	17	3.7	12	0		75	5	5	3	+	
11 N, 5 S	15.4	8.4	9	1.7	1.35	84.7	8.7	8.1	6.8	4 —, 11 +, 1 A C	38.7

When we examine the averages for the tuberculous patients, we apparently approach certain correlations of significance. It will be observed that the permeability of the capillaries increases and the blood calcium diminishes (as does the K/Ca ratio). The Kromayer light erythema time, the ice reaction time and the NaCl test (McClure-Aldrich) time are lessened, as we pass from the gaining to the losing groups. In a previously published analysis,² we showed the differences in the curves of the blood pressure following the injection of epinephrine and the change in the leukocyte count following injections of a non-specific milk preparation in these groups of patients. These curves

² Petersen, W. F., and Levinson, S. A. *Am. Rev. Tuberc.* **18**: 616 and 839, 1928.

TABLE 5—Results of Examinations of Patients Who Were

Patient	Diagnosis	Weight	Condition at Time of Writing	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Globulin, per Cent	Protein, per Cent
53	M A B	Stationary	Losing	6	71.5	11.5	12.9	24	1.85	45	8.8
63	F A C	Gaining	Losing	7	82	11.7	10.2	17.2	1.63	36	9.9
69	F A B	Gaining	Dead	6	67	11.1	10	13.9	1.39	60	9.35
49	M A B	Gaining	Dead	7.5	44	5.8	8.6	22.4	2.6	40	9.9
83	F A B	Gaining	Dead	6	74.7	12.4	13.1	21.6	1.65	23	8.67
67	F A B	Gaining	Losing	6	58	9.6	11.6	19.2	1.65	60	10.7
64	F A B	Gaining	Dead	6	56.4	9.4	12	19	1.59	30	10.6
68	M A A	Gaining	Dead	9	32	3.5	10.6	14.3	1.35	20	8.06
34	F A B	Stationary	Dead	7	42	6.1	9	19.1	2.13	23	8.6
58	F A B	Gaining	Stationary	7	45	6.4	11	17.4	1.57	17	11
56	M A A	Gaining	Stationary	8	67	8.3	8.6	18.1	2.1	15	7.79
Averages				6.8	58.1	8.7	10.6	18.7	1.77	34.2	9.39

TABLE 6—Results of Examinations of Tuberculous Patients

Patient	Diagnosis	Condition at Time of Examination	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Ery- thema Time, Min
37	M A A	Arrested	9	60.7	6.7	11.4	23.7	2.08	10	8.7	33
41	F A B	Improved	7.5	78	10.4	11.4	24	7.85	34	7.85	147
75	F A A	Improved	6	62.3	10.3	10.3	17.6	1.71	100	9.33	
77*	F A B	Improved Quiescent	6	43	7.1	10.8	21.6	1.98	5	12.9	
73	M A A		6	63.1	10.5	11.6	17.6	1.53	35	9.35	
65	M A A					12.2	23.8	1.95	23	9.56	110
42	F A B	Well Stationary	6	65	10.9	9.5	16.6	1.75	50	10.4	60
62	F A A		6	69	11.5	8.2	14.4	1.75	7	7.73	85
70	F A B		6	37.7	6.2	13.4	23.9	1.79	45	11.27	
59	F A B		6	68.4	11.4				15	9.35	190
19	F A A	Wassermann ++ Quiescent	8	56	8.3	8.8	18.9	2.15	22	7.93	50
30	M A A		6	88	14.6	10.8	17	1.57	40	7.91	170
23	F A A		8	76	9.5	9.5	23.1	2.43	30	8.56	140
24	M A B	Quiescent	8.5	72	8.4	8.4	24.5	2.92	10	7.85	80
32	F A A	Arrested Quiescent	7	72.1	10.3	9.5	15.6	1.64	25	8.23	142
40	F A B		7.5	69.3	9.2	8.8	22.4	2.55	45	6.43	70
38	F A B	Arrested	7	65.6	9.3	9.3	26.8	2.88	10	8.06	130
29	Min A	Arrested	9	60.7	6.7	11	18.6	1.69	25	8.7	237
1	M A A	Improved	8	74	9.3	10.2	15.2	1.51	5	7.63	45
5	M A B	Stationary	8.5	75	8.8	9.1	15.4	1.69	32	8.5	90
Averages			7.1	66.4	9.44	10.1	19.8	1.97	28.4	8.817	111

* Died, 1929

Doing Well When Examined but Who Subsequently Grew Worse

Kromayer Light Py- thema Time, Min	Reaction to Ice, Seconds	CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm	Epinephrine, Flare, Radius, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Mm	Reaction to Tuberculin, Mm			Tuberculosis Fixation	Corpuscles/Plasma
										24 Hours	48 Hours	72 Hours		
120	15	51.9	Vagotonic	15.7	7	12	0	1.30	90	7	8	4	+++	38.4
23	12	53.5	Vagotonic	14.2	6.7	12	0	1.21	130	10	10	0	—	44.3
25	10	59.8	Sympatheti- cotic	13	4.2	0	3.5	1.16	33	6	5	4	+++	37.1
78	19	57.3	Vagotonic	7.2	8	10	2.5	1.04	85	10	9	0	+++	35.5
	8	56.3	Vagotonic	20.7	6.5	10	4		45	21	12	8	—	32.1
40	23	58.9	Sympatheti- cotic	16.5	10.1	12	1	1.05	30	4	4	6	++++	34.6
65	15	56.3	Sympatheti- cotic	17.7	8.1	10	5	1.23	90	11	3	2	++++	38.2
110	15	55.4	Sympatheti- cotic	8	4.7	14	0	1.22	110	8	8	6	—	33.1
71	1	62.7	Sympatheti- cotic	13.7	6.6	10	9	1.62	85	8	0	0	+++	42.9
65	6	65	Vagotonic	16	4.5	12	0	1.4	159	7	15	8	—	19
85	10	50.4	Vagotonic	10.7	8.2	12	0	1.32	120	10	6	6	++++	48.8
74.4	12.1	57.8	6 V, 5 S,	13.9	6.7	11.1	2.27	1.25	89	9.2	6.8	4	7+, 4—	37

in Whom Disease Was Stationary and Remained So

Reaction to Ice, Seconds	CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm	Epinephrine, Flare, Radius, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Mm	Reaction to Tuberculin, Mm			Tuberculosis Fixation	Corpuscles/Plasma
									24 Hours	48 Hours	72 Hours		
7	58.7	Vagotonic	16.7	9.5	7	1.5	1.25	33	2	5	8	—	43.2
12	49.8	Vagotonic	15.5	6.6	6	5	1.53	83	10	25	8	—	37.5
18	53.5	Sympatheti- cotic	10.75	7.25	6	0	1.30	145	28	12	6	++++	34.3
25	55.4	Vagotonic	11.5	5	14	0	1.35	83	11	8	6	++++	31.1
15	59.3	Vagotonic	18.25	5.75	13	1.5	1.15	60	6	8	4	+++	36.05
12		Vagotonic	11.7	5.7	7	0	1.38	85	8	5	3	+	45.1
20	63.8	Vagotonic	17.5	11.8	7	14	1.73	75	22	10	3	—	46.7
30	47.9	Vagotonic	17.5	4.75	15	0	1.07	85	12	22	0	+++	54.2
3	52.9	Vagotonic	5.2	3.1	6	0	1.03	68	6	7	8	+++	40.1
10	53.7	Sympatheti- cotic	7.5	3.1	11	2	1.3	80	5	10	0	—	29
12	54.4	Vagotonic	19.2	6.6	5	10	0.92	92	7	7	0	+	44.5
15	51.4	Sympatheti- cotic	25.5	10.2	10	0	1.05		14	3	0	—	36.4
8	68	Sympatheti- cotic	12.5	6.3	5	1.5	1	40	3	3	0	++++	41.3
5	66	Sympatheti- cotic	15.5	6.6	9	3	1.09	190	5	0	0	—	41.1
12	43.9	Vagotonic	18.5	8	20	5	0.98		3	0	0	—	47.1
8	56.9	Vagotonic	17	5.8	10	5	1.84	35	0	0	0	++	43.1
5	57.2	Vagotonic	23.7	9.5	10	12.5	1.43	80	0	0	0	+	35.1
8	40.1	Vagotonic	14	6.75	4	3	0.95	65	10	6	7	—	51.1
15	58.6	Vagotonic	17.5	6.5	9	0	1.06		0	0	0	—	42
15	57.2	Vagotonic	7.7	3	6	0	1.05	70	20	0		—	45.2
12.7	55.1	15 V, 5 S	15.16	6.59	9	3.2	1.223	83.7	8.6	6.5	2.6	10+, 9—	41.2

showed a consistent increase in the vagotonic effect in the losing groups. The mathematical calculation of the pulse pressure following the injection of epinephrine shown in table 3 merely indicates the decided difference existing between the actively tuberculous groups and the

TABLE 7—Results of Examinations of Tuberculous Patients Who

Patient	Diagnosis	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Try theme Time, Min	Reaction to Ice, Seconds	CO ₂ Combining Power
22	M A A	7 5	81 7	10 8	9 5	22 1	2 33	29	7 1	18	2	74
33	M A B	8	62	7 7	10	16 3	1 63	25	7 8	75	15	53 7
36*	F A A	6	76	12 6	9 9	26 2	2 67	43	8 9	111	12	55 3
51	M A B	5 1	68 5	9 7	9 9	20 3	2 05	50	10 5	90	8	66 8
Averages		6 6	72	10 4	9 8	21 2	2 17	44 2	8 5	73 5	9 2	62 4

* Died, November, 1928

TABLE 8—Results of Examinations of Tuberculous Patients

Patient	Diagnosis	Condition at Time of Writing	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light 1 ry theme Time, Min	Reaction to Ice, Seconds
9	M A A	Dead	8	72 4	8 04	10 2	19 1	1 87	9	8 28	15	2
18	F A A	Dead	8	75	9 4	8 4	21 7	2 58	75	8 8	10	3
61	F A C	Dead	6	69	11 5	10 5	18 8	1 79	43	10 2	30	10
47	F A A	Dead	6 4	73	11 2	10 9	20 3	1 85	28	9 45	105	12
66	F A C	Dead	8	82	11 5	10 2	19 6	1 92	50	9 66	95	16
60	F A C	Dead	7 5	79	10 5	11 1	19 2	1 73	48	8 70	90	20
78	M A B	Dead	7	73	10 7	10 4	19 2	1 84	15	9 87		13
48	M A B	Dead	7 5	62 5	8 2	8 5	16 2	1 91	40	9 92	115	8
74	F A B	Dead	6	58	9 6	10 1	17 9	1 72	46	8 06		5
28	F A A	Dead	7	75	10 7				50	8 92	163	9
25	F A A	Dead	8	74	9 3	9 9	15 4	1 56	67	7 73	93	12
7	M A B	Dead	8 5	71	8 3	9	14 3	1 59	31	7 36	8	5
15	F A A	Stationary	8	75	9 3	9 7	19 4	2	32	8 36	40	4
26	M A B	Dead	4 5	70	15 4	11 4	17 3	1 52	35	8 28	193	20
31	M B	Stationary	7	74 2	10 6	12 8	15 7	1 23	42	9 02	156	8
Averages			7 1	72 2	10 2	10 2	18 1	1 79	42 7	8 84	85 6	9 8

group of "normal" persons, the group of persons with "healed" lesions and the group with roentgen evidence of "active" tuberculosis.

On the other hand, the values for globulin follow more consistently the clinical classification, as do those for the Daranvi reaction, the complement fixation, the basal metabolic rate, etc.

While the analysis based on the weight curve enables us to reach certain definite conclusions, the weight curve alone is by no means a

criterion of resistance. Apart from the fact that periodic fluctuations may depend solely on fluctuation of the water balance, patients may be gaining at the time of the examination and shortly afterward present a reversal.

Were Losing Weight and Who Subsequently Showed Improvement

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm	Epinephrine, Flare, Radius, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Min	Reaction to Tuberculin, Mm			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
Vagotonic	15	8.6	6	2.5	1.06	45	8	12	0	++	32.6
Sympatheticotonic	11.5	6.75	8	2.5	1.6	93	11	0	0	—	39.1
Sympatheticotonic	16.2	6	10	5	1.64	95	12	4	0	++++	46.5
Sympatheticotonic	11.5	6.1	10	11.5	1.64	95	12	4	0	++++	40.7
3 S, 1 V	13.5	6.8	8.5	5.25	1.43	82	8.2	5	0	3+, 1—	39.7

Who Were in Poor Condition and Who Grew Worse

CO ₂ Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm	Epinephrine, Flare, Radius, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Cholesterol/Lecithin	NaCl Test (McClure- Aldrich), Min	Reaction to Tuberculin, Mm			Tuberculosis Fixation	Corpuscles/Plasma
								24 Hours	48 Hours	72 Hours		
62.1	Vagotonic	18	5	6	4.5	1.18	75	0	0	0	—	46
55.1	Sympatheticotonic	17	6.8	5	4	1.05	45	6	7	10	+	34.5
42.5	Sympatheticotonic	15.7	4.7	7	0	1.31	75	5	6	8	+++	45.5
55.2	Vagotonic	10.5	6.3	8	18.5	1.2	105	7	7	7	+	40.7
53.5	Vagotonic	12	5.7	12	0	0.94	75	9	9	7	++	34.3
38.8	Vagotonic	15.2	5.5	10	0	1.18	65	7	5	3	—	51.1
57.5	Sympatheticotonic	12.5	6	10	1	1.33	18	8	6	3	—	37.1
57.2	Vagotonic	15.2	13	9	11	1.65	90	8	4	3	++++	44.1
60.3	Vagotonic	15	5.7	14	0	1.24	48	9	3	0	+	34.8
59.2	Vagotonic	23.5	5.3	8	0	1.1	80	7	3	0	+++	36
51.8	Vagotonic	12.7	5.6	10	5.5	1	87	7	0	0	+++	30.9
57.2	Vagotonic	17	5.7	4	5.5	1.13	40	5	0	0	—	37.3
62.5	Vagotonic	20.5	6	9	2.5	1.12	50	0	0	0	—	37.7
57.2	Vagotonic	11.25	5.7	5	7.5	1.17	52	4	0	0	+++	38
57.2	Vagotonic	14.5	5.37	10	5	1.05	15	5	0	0	—	46.1
55.1	12 V, 3 S	15.37	6.35	8.4	4.3	1.17	61.3	5.8	3.3	2.7	9+, 6—	39.6

SUMMARY BASED ON PROGNOSIS

The patients of the series studied were examined during the summer of 1927. As all were sanitarium patients, it was possible to follow the clinical course of the disease in each and to analyze the results of the examinations on the basis of the condition in 1929. In tables 4 to 8, we present the results of the more important examinations of these patients when so classified.

When we examine the summaries in table 9 certain deductions appear warranted

Lower Capillary Permeability in Patients with Good Prognosis—While occasionally increased permeability is found in persons of this type (no 44 and 55 in the group who were gaining—both, however, with pleuritic effusion), generally, as we showed previously, it goes hand in hand with progression of the disease, while persons with silent lesions (the ones with roentgen evidence of active tuberculosis in the series of 100 "normal" men) have low permeability

TABLE 9—*A Summary of the Results of Examinations*

Table	Number in Group	Condition at Time of Examination	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	K / Ca Ratio	Globulin, per Cent
4	16	Good, continued improvement	7.5	67.3	9.3	10.7	18.5	1.75	33
5	11	Good, later poor	6.8	58.1	8.7	10.6	18.7	1.77	34
6	20	Stationary	7.1	66	9.4	9.1	19.8	1.97	38
7	4	Poor, later improved	6.6	72	10.4	9.8	21	2.17	44
8	15	Poor, continued extension	7.1	72	10.2	10.2	18.1	1.79	42.7

For many reasons, a question of utmost importance immediately comes up. Is the increased capillary permeability that is associated with poor prognosis and progression of the disease due to the clinical condition or does the increased permeability bring about the progression? If the former, we deal merely with an incident of clinical observation, if the latter, we have at our command an approach to one of the factors in therapeutic control. This is discussed in part VIIC. The clinical association is obviously close. In the group who were doing well when first examined and who later showed decline (table 5), the capillary permeability was low. In the group who were doing poorly when first examined and who showed subsequent improvement (table 7) capillary permeability was high.

The status of the capillary wall—the functional capacity—is obviously a most labile affair, depending not only on the activity of the

local tissue, but on endocrine (probably thyroid-suprarenal-pituitary) and chemical equilibriums, as well as on autonomic disturbances. With so many variable factors, one cannot assume any dogmatic position. Certainly, acute intoxications increase the capillary permeability.³ Presumably, tuberculin may diminish as well as increase it.⁴ Progression of the disease might logically be expected to increase permeability. On the other hand, there is evidence to support the view that the status of the capillary may be the predetermining factor on which either fixation or dissemination depends. We have mentioned the relation to

of Tuberculous Patients (Tables 4 to 8)

Vascular Reaction to Epinephrine		Epinephrine, Wheal, Diameter, Mm	Epinephrine, Flare, Radius, Mm	Thyroxin, Wheal, Mm	Thyroxin, Flare, Mm	Cholesterol/Leethin	NaCl Test (McClure- Aldrich), Mm	Reaction to Tuberculin, Mm			Tuberculosis Fixation	Corpuscles/Plasma
								24 Hours	48 Hours	72 Hours		
11 Vagotonic	= 30%	15.4	8.4	9	2.6	1.35	84.7	8.7	8.1	6.8	70	38.7
5 Sympatheticotonic												
6 Vagotonic	= 45%	13.7	6.7	6.7	2.2	1.25	89	9.2	6.8	4	63	37
5 Sympatheticotonic												
15 Vagotonic	= 25%	15.1	6.6	9	3.2	1.22	83.7	8.6	6.5	2.6	52	41.2
5 Sympatheticotonic												
1 Vagotonic	= 75%	13.5	6.8	8.5	3.2	1.43	82	8.2	5	0	75	39.7
3 Sympatheticotonic												
12 Vagotonic	= 20%	15.3	6.3	8.4	4.3	1.17	61.3	5.8	3.3	2.7	60	39.6
3 Sympatheticotonic												

season. A similar case may be made out for the menstrual cycle, for remote trauma and for inanition. But, again, we must not forget that in thyroid disease, with its accompaniment of greatly increased permeability, no direct relation to activation of tuberculosis exists.

Lowered Inflammatory Index in Cases with a Favorable Prognosis—While the differences are not great, the grouping shows conclusively that the inflammatory response of the skin in patients doing well is seemingly diminished. In the introductory paragraphs, we presented our reasons for believing that such a lowering of the inflammatory response may be of benefit to the patient in protecting him from too

³ Petersen, W. F. Permeability of Skin Capillaries in Various Clinical Conditions, *Arch. Int. Med.* **39**:19 (Jan.) 1927.

⁴ Petersen, W. F., and Levinson, S. A. *Am. Rev. Tuberc.* **8**:122, 1923, *J. Immunol.* **8**:387, 1924.

great an absorption of toxic material. Many coordinated problems enter into consideration, because certain types of tuberculous lesions may be observed in which inflammatory response may be most useful (skin, etc.) Generally speaking, the clinician has tried to build up a resistance to inflammatory response, either by immunizing his patient until the reaction of the skin has diminished in intensity or by using non-specific methods to bring about the same result. The therapeutic goal in common practice is distinctly inhibitory, even when brought about by the methods which may transiently accelerate the inflammatory response.

High Blood Calcium Level in Cases with Good Prognosis—The explanation of the calcium values is, we believe, relatively simple. The cases with good prognosis have a high level, with progression this declines. In cases that have a poor prognosis, calcium is evidently swept into the serum from the tissues and raises the level in the serum. We have already seen that there is no relation of the calcium level to the clinical status when the results of the examinations of the patients are arranged on the basis of the classification made by the National Tuberculosis Association. When the results are arranged on the basis of the weight curve, the patients who are gaining show a higher calcium level. There appears to be no necessary relation to the K/Ca ratio.

High Serum Globulin in Cases with Poor Prognosis—As an index of activity, the increase in globulin—and with it a coincident increase in the degree of positiveness in such a reaction as the Darányi reaction—is, as might be expected, clearcut. The concentration of serum protein, is, on the other hand, not particularly characteristic.

Apparently Sympatheticotonic Reactions to Epinephrine—In a previous study of the curves of the reactions of these patients to epinephrine, we called attention to the fact that when the results are grouped on the basis of the weight curve, the patients who are gaining are shown to have a less marked vagotonic reaction than those who are losing. In the tables here presented, we have merely indicated the general character of the curves by designating those as sympatheticotonic in which a primary increase in the systolic blood pressure can be ascertained in the first fifteen minutes after a subcutaneous injection of epinephrine hydrochloride.

In our series of 100 "normal" men, approximately 40 per cent give a distinctly sympatheticotonic reaction⁶. In the tuberculous group, 32 per cent were so classified. But when we estimate effects on the basis of the actual increase in pulse pressure, the 100 "normal" men show an

5 Petersen, W. F., and Levinson, S. A. *Am. Rev. Tuberc.*, to be published.

6 Petersen, W. F., Levinson, S. A., and Arquim, S. *Relation of Reaction to Epinephrine to Potassium Calcium Ratio and Other Ratios*, *Arch. Int. Med.* **42** 256 (Aug.) 1928.

average increase of approximately 14 per cent during the hour after the injection, while the tuberculous persons show an actual loss of 5 per cent

In general, it appears that there are more sympatheticotonic reactions among the patients with favorable prognoses. We desire, however, that this conclusion be regarded with reservation. The reactions to epinephrine by no means conform to the fixed or rigid outlines formerly accepted. When one examines the individual curves, one is rather struck by the irregularity in the tuberculous person as compared with the "normal" person. We believe that this is an expression of the general autonomic instability. In the series of four patients who were losing and who later improved (table 7) there is an observation that may be of some significance. Of the four, three had a distinctly sympatheticotonic reaction. Whether this presaged the later favorable development we do not know.

The Bearing of the Intracutaneous Reactions—Of the intracutaneous reactions, only the flare due to the injection of thyroxin seems to be of interest. The persons with favorable prognoses appear to be less reactive. This may be in line with the general diminution of the inflammatory reaction, it may be related to the same phenomena that underlie the delay in their reaction to ice and the lessened permeability of their capillaries (see table 1 part I).

Larger Value for the Cholesterol/Lecithin Ratio in Persons with Favorable Prognoses—A distinct correlation exists between the clinical condition and the cholesterol/lecithin ratio, an exception being found only in the group shown in table 7. Here a high value of the ratio existed with a declining weight curve at the time of examination. Just as with the reaction to epinephrine the possibility exists that this reaction is of some prognostic significance. The assumption that the outcome of the reaction to epinephrine may depend on the cholesterol/lecithin ratio is unfounded. Our sympatheticotonic patients show both high and low values for this ratio.

Shortening of the McClure-Aldrich Sodium Chloride Disappearance Time in the Cases with "Poor" Prognosis—This is apparent in the tables in which the results are arranged in accordance with the weight curve, as well as in the final arrangement on the basis of prognosis. On the other hand, the fallacy inherent when only the N T A clinical classifications are used becomes apparent when we study table 1. Here the far advanced "C" cases (five in number) have an average disappearance time of 93 minutes, i.e., longer than that of any of the other groups. However, the three members of this group who died had a 75 minute disappearance time, while the two still living had a prolonged time of 130 and 110 minutes, respectively. The average, of course, gives an entirely wrong impression. It would appear that the reaction might serve a useful purpose in the prognosis.

Cases with Favorable Prognosis Characterized by a More Marked Reaction to Tuberculin—Both in the size of the wheal and in the persistence of the infiltration, the patients with the favorable prognoses reveal a considerable accentuation. On the other hand, there is no characteristic difference in the circulating antibodies (complement fixation) nor any striking difference in the corpuscle/plasma ratio.

ANALYSIS OF RESULTS IN FATAL CASES

Finally, we present an analysis of the results of the examinations in cases that have terminated fatally. During the twenty months that elapsed between the time of the examination and the time of this analysis,

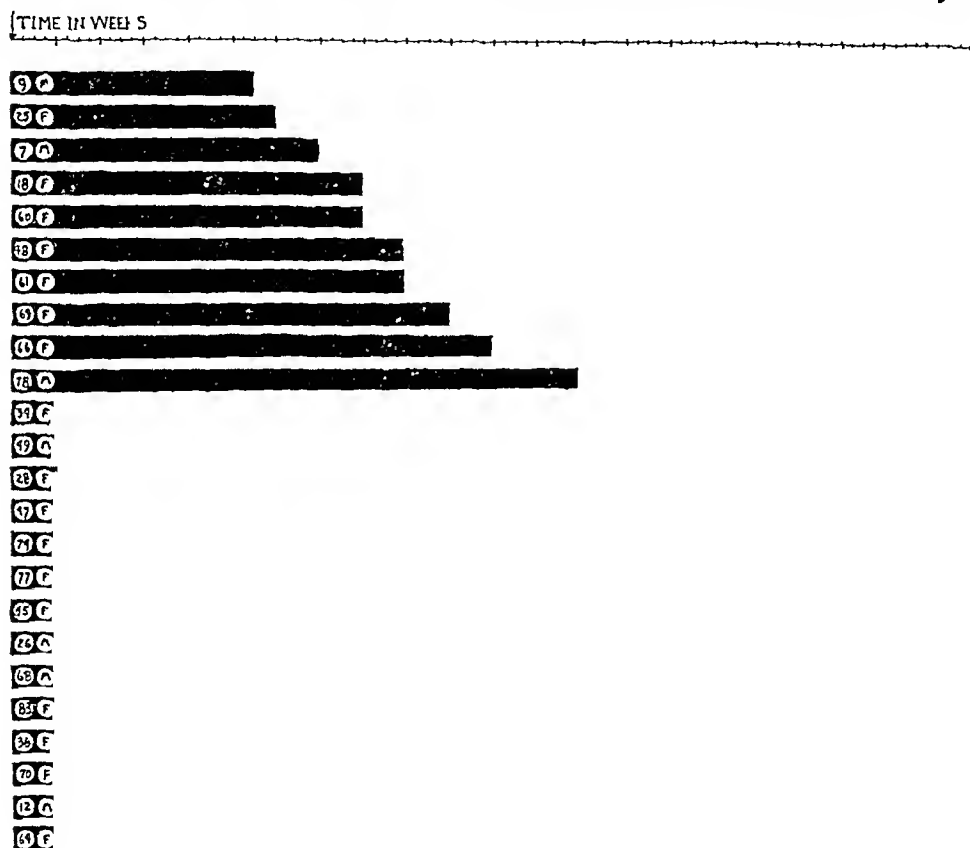


Chart 1—Fatal cases. The duration of the illness from the time of examination to the time of death (in weeks). *F* means far advanced, *M*, moderately advanced. The numbers are the case numbers.

twenty-four patients died either in the hospital or elsewhere in the city. Two with far advanced tuberculosis left the city and they probably died, but we have not included them in the group.

In the chart the duration of life after the time of the examination is indicated by the length of the column. The number of the patient and the type of the case at the time of the examination (*F*, far advanced, *M*, moderately advanced) are noted in the circles.

In table 10, the more interesting data have been collected. An average has been made for the twelve patients living for the shorter periods.

to be contrasted with that for the group of twelve who died later. The total period of clinical activity until the time of death averaged 45 months for the former group and 65 months for the second group.

An examination of the table indicates the following. The first group, the short lived ones, had the more permeable capillaries (67 as compared

TABLE 10—Results of Examinations of Patients with Fatal Tuberculosis, One Group Short Lived and the Second Group Longer Lived

Patient	Total/Time of Activity Until Death, Mo	Capillary Permeability	Calcium, Mg per 100 Ce	Potassium, Mg per 100 Ce	K / Ca Ratio	Globulin, per Cent	Cholesterol, Mg per 100 Ce	Lecithin, Mg per 100 Ce	Reaction to Tuberculin			NaCl Test (McClure- Aldrich), mm	Reaction to Ice, Seconds	Reaction to Epinephrine
									24 Hours	48 Hours	72 Hours			
9	29	72	10.2	19.1	1.87	9	208	17.5	0	0	0	75	2	Vagotonic
25	35	74	15.4	15.4	1.56	67	171	17.1	7			87	12	Vagotonic
7	14	71	9	14.3	1.59	31	190	16.7	5			40	5	Vagotonic
18	13	75	8.4	21.7	2.58	75	167	15.8	6	7	10	45	3	Sympathetic cottonic
60	35	79	11.1	19.2	1.73	48	196	16.6	7	5	3	65	20	Vagotonic
48	75	62.7	8.5	16.2	1.91	40	222	13.4	8	4	3	90	8	Vagotonic
61	75	69	10.5	18.8	1.79	43	230	17.8	5	6	8	75	10	Vagotonic
69	65	67	10	13.9	1.39	60	171	14.7	6	5	4	35	10	Vagotonic
66	50	82	10.2	19.6	1.92	83	163	17.2	9	9	7	75	16	Vagotonic
78	25	73	10.43	19.2	1.84	15	208	13.3	8	6	3	18	13	Sympathetic cottonic
34	40	42	9	19.1	2.13	28	167	10.7	8	0	0	85	1	Sympathetic cottonic
49	31	44	8.6	22.4	2.60	40	155	14.9	10	9	0	85	19	Vagotonic
Av	45	67	9.6	18.2	1.9	45	188	15.4	6.6	4.2	3	64	12	9 V / 3 S
28	90	75				50	167	15.1	7	3	0	80	9	Vagotonic
47	50	73	11.2	20.3	1.85	23	167	13.9	7	7	7	105	12	Vagotonic
74	50	58	10.1	17.9	1.72	46	196	15.7	9	3	0	48	5	Vagotonic
77	62	43	10.8	21.6	1.93	5	278	20.6	11	8	6	83	25	Vagotonic
45	41	65	11.8	20.6	1.74	40	208	14.7	9	11	13	62	20	Vagotonic
26	55	70	11.4	17.3	1.52	35	185	15.8	4	0	0	52	20	Vagotonic
63	31	32	10.6	14.3	1.35	20	238	19.5	8	8	6	110	15	Sympathetic cottonic
83	47	74	13	21.6	1.65	26	167		21	12	8	45	8	Sympathetic cottonic
36	92	76	9.9	26.2	2.67	43			2	4	0	95	12	Sympathetic cottonic
70	130	37.7	13.4	23.9	1.79	45	167	16.1	6	7	8	68	3	Vagotonic
12	80	72	10.7	19.2	1.79	32	208	20.8	6	0	0	55	4	Sympathetic cottonic
64	45	56	12	19.1	1.59	30	208	16.8	11	3	2	90	15	Sympathetic cottonic
Av	65	61	11.4	20	1.8	34	199	16.9	8.5	5.5	4.1	74	15	7 V / 5 S

with 61). They have a lower level of blood calcium (9.9 as compared with 11.3) and less potassium (18.2 as compared with 20), but a slightly higher value for the K/Ca ratio. The serum globulins are increased 45 per cent as compared with 34 per cent, while both the cholesterol and the lecithin levels are lower. The reaction to tuberculin is less marked (6.6, 4.2 and 3 mm for twenty-four, thirty-six and seventy-two hour readings, as compared with 8.4, 5.5 and 4.1 mm). The McClure-Aldrich sodium chloride disappearance time is shorter, as is also the time of the reaction to ice.

When we turn to the reaction to the subcutaneous injection of epinephrine hydrochloride, the results in the cases of rapidly fatal disease are of considerable interest. The results are preponderatingly vagotonic, while those in the cases in which the patients lived longest were generally sympatheticotonic.

B DETAILED STUDY OF THE REACTIONS OF PERSONS WITH TUBERCULOSIS

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Permeability of the Capillaries
Inflammatory Index
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Vascular Reactions to Epinephrine
CO ₂ Combining Power
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Lecithin
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BLISTER TIME

In a study of the blister time of tuberculous persons in relation to our group of 100 "normal" men, we pointed out that the persons with roentgen evidence of active tuberculosis (chronic) have, in general, a longer blister time, and in a previous study,¹ we demonstrated that the blister time of those with moderately advanced tuberculosis was prolonged over that of the 100 "normal" men, but that, with advance of the disease, the blister time shortened progressively. The average blister time of our group of 100 "normal" men was 7.5 hours, for the twenty truly normal persons in this group, it was 6.8 hours. For those with roentgen evidence of active tuberculosis, it was 8.4 hours, and for the group of eighty-three tuberculous patients it was 7.4 hours.

To obtain a survey of the relation of the blister time of the tuberculous patients to the clinical status and to the status in the other tests,

1 Levinson, S. A., and Petersen, W. F. *Am Rev Tuberc* 15:681, 1927.

we have prepared chart 1, as well as a table of averages for the results of the examinations of the twenty persons with the shortest, and the twenty with the longest blister time

Explanation of Charts—As chart 1 is typical for the other charts of this series, we shall explain it in some detail

The original blister time curve for the clinical material used in the study reported in part III has been retained. It begins with an individual blister time of 3.5 hours and ends with a group blister time of 15 hours. The diamond indicates the range of the blister time of the truly normal persons, extending from a "low" of 6 to a "high" of 9 hours. In addition, symbols at the bottom designate the position on

TABLE 1—*Comparison of the Groups with the Short, the Medium and the Long Time for the Appearance of the Cantharides Blister, with Regard to Clinical Status*

Clinical Classification of Patients	Short Blister Time (20 Patients)	Medium Blister Time (37 Patients)	Long Blister Time (20 Patients)
As to Type of Tuberculosis			
Minimal	10%	16%	35%
Moderately advanced	25%	27%	45%
Far advanced	65%	57%	20%
	100%	100%	100%
As to Prognosis			
Good	25%	27%	50%
Fair	40%	35%	20%
Poor	35%	38%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	35%	45%
Stationary	45%	40%	30%
Losing	10%	19%	25%
	100%	100%	100%

this original curve of the truly normal persons and these showing healed and those giving roentgenologic evidence of active tuberculosis

On this original curve, we have superimposed the curve of the determinations made on the eighty-three tuberculous patients, and have recorded their individual numbers on the curve. Adjacent symbols indicate (X) the death of the patient² or (#) that there was pleural effusion

In the horizontal columns at the top of the curve, we have indicated the clinical status of the patient. For instance, the first patient represented on the curve (no 26) is recorded as having had a moderately advanced tuberculosis with a poor general prognosis, and as being stationary in weight when examined

When we examine the curve, we find that the range of the blister time is from 4.5 to 14 hours, that patients with pleural effusion appear

² Patients 26, 70, 64, 36 and 12 died after the charts were in the hands of the printer. The symbols for these have therefore not been recorded

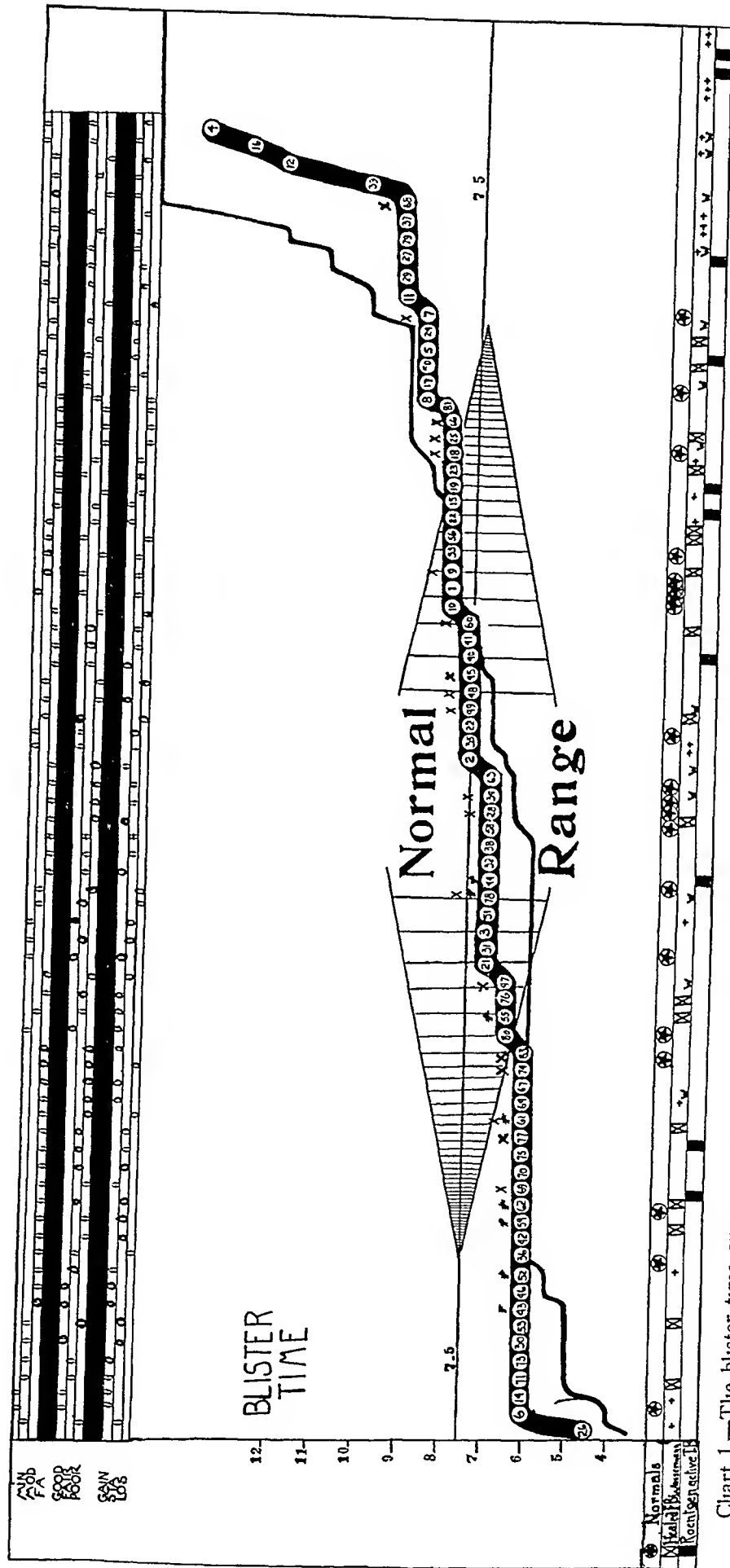


Chart 1 —The blister time curve in patients with tuberculosis. The curve has been superimposed on the original blister time curve for the miscellaneous clinical groups of part III. The original curve begins with a blister time of 3.5 hours, shown by one person, and ends with a blister time of 15 hours, which was shown by a group. The diamond indicates the range of the blister time in the truly normal persons (from 6 to 9 hours). The symbols at the bottom designate the positions on the original curve of the truly normal persons, the persons showing healed tuberculous lesions and those giving roentgen evidence of active tuberculosis.

The individual numbers of the eighty-three patients with tuberculosis are recorded on this curve, the adjacent symbols indicating (X) a patient who died, and (#) one that showed pleural effusion. In the horizontal columns at the top, the clinical status of each patient is indicated. All succeeding charts in this part of the paper are constructed similarly.

at the lower end of the curve and that those who died are apparently uniformly scattered

In analyzing the results of the examination under consideration in relation to the clinical conditions, we have arbitrarily selected twenty at each end of the curve and have compared them with the middle group. This analysis gives the results shown in table 1. It is evident that the

True Normal Group
Roentgen Healed Tuberculosis Group
Roentgen Active Tuberculosis Group

Minimal A Group
Minimal B Group
Moderately Advanced A Group
Moderately Advanced B Group
Far Advanced A Group
Far Advanced B Group
Far Advanced C Group



Chart 2—The blister time curve in the 100 "normal" men of part I

TABLE 2—Comparison of the Averages for the Results of the Examinations of the Groups with the Shortest and the Longest Blister Times

Blister Time, Hours	Globulin (per Cent of Total Protein)	Protein, Mg per 100 Cc	Ice Reaction, Seconds	Reaction to Epinephrine, Flare, Mm	Reaction to Thyroxine, Wheal, Mm	Reaction to Tuberculin at 24 Hours, Mm	Deaths
5.92	38.66	9.32	13.9	7.22	9.55	9.4	7
9.3	31.4	8.5	10.8	5.91	7.8	7.5	6

group with the short blister time includes more persons with far advanced tuberculosis, and the group with the prolonged blister time more patients with a good prognosis. In the latter group, the percentage of those losing weight is somewhat greater.

The averages for the more significant reactions of the twenty patients with the shortest blister time are compared with those of the twenty with the longest blister time in table 2.

When we compare the different groups of the 100 "normal" men, as well as the tuberculous groups in relation to blister time, we obtain a picture (chart 2) similar to that which we previously described, i e, the group with healed tuberculous lesions and the group with roentgenologic evidence of active tuberculosis (the latter chronic and silent) have a longer blister time than have the normal persons. Among the persons with active tuberculosis, those with the minimal and moderate manifestations have a longer time than those in whom the disease is far advanced, whose blister time progressively shortens.

PERMEABILITY OF THE CAPILLARIES

When we examine the permeability curve (chart 3), we note that the cases of the "normal" group that gave roentgenologic evidence of active tuberculosis (lowest horizontal line) are represented in the low range of the curve. On the other hand, those in the series of

TABLE 3—*Comparison of the Groups with the Low, the Medium and the High Permeability of the Capillaries, with Regard to Clinical Status*

Clinical Classification of Patients	Low Permeability (20 Patients)	Medium Permeability (37 Patients)	High Permeability (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	16%	20%
Moderately advanced	20%	43%	25%
Far advanced	50%	41%	55%
	100%	100%	100%
As to Prognosis			
Good	45%	27%	30%
Fair	30%	37%	40%
Poor	25%	36%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	40%	40%
Stationary	27%	40%	35%
Losing	33%	20%	25%
	100%	100%	100%

eighty-three tuberculous patients, who died, appear in equal numbers at both ends of the curve. However, the duration of clinical activity, as brought out in table 10 of part VII A, is markedly different.

The patients with pleural exudate are, with one exception (no 52), found toward the upper end of the curve. The association of exudative reactions and increased permeability seems evident.

In examining for the relation between the clinical status and the permeability of the capillaries, percentages were determined as recorded in table 3. No striking differences are revealed in this classification, the group with less permeable capillaries has the largest percentage with good prognosis, but no significant relation of permeability to gain or loss in weight is shown.

Table 4 brings together the averages for the more significant reactions of the twenty persons with low and the twenty with high permeability.

In the group with low permeability the blister time is somewhat longer, the calcium level is higher, the value of the K/Ca ratio is lower, the total protein is greater but the globulins are less, and the time for the absorption of the salt solution is somewhat longer

In previous papers we called attention to the relation of capillary permeability to tuberculosis—the association of increased permeability with clinical progression, etc. The results of the examinations recorded here confirm our previous work

TABLE 4—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Permeability of the Capillaries*

Capillary Permeability	Blister Time, Hours	Calcium, Mg per 100 Cc	Potassium, Mg	K/Ca Ratio	Protein, Mg	Globulin, per Cent of Total Protein	Reaction to Tuberculin at 24 Hours, Min	CO ₂ Combining Power	NaCl Solution Absorption, Minutes	Deaths
54 78	7.7 7.1	10.6 10.3	19.3 20.2	1.8 2	9.92 8.4	25 36	8.7 8.3	55.5 57.5	80 70	7 6

INFLAMMATORY INDEX

In the foregoing studies of blister time and capillary permeability, it was shown that short blister time and high permeability were, in general, associated with activity. The inflammatory index, taking both factors into consideration (permeability/blister time), merely confirms this general observation.

When we examine chart 4, we observe that the inflammatory index of the entire tuberculous group is somewhat greater than that of the group of "normal" persons and miscellaneous clinical patients, and we find the majority of those who died, as well as of the patients with effusion, having an inflammatory index above the normal average of 8.2. The persons who gave roentgenologic evidence of active tuberculosis appear toward the lower end of the curve.

When we analyze the twenty cases of low inflammatory index, the thirty-seven of intermediate index and the twenty of high index in relation to clinical status, we obtain the percentages set forth in table 5. It is apparent that the cases of far advanced tuberculosis more frequently occupy the middle and the high range of the curve, that the prognosis is better at the low end and poorest in the higher region and, finally, that gain or loss in weight is not directly related.

In examining table 6 in which a comparison is made between the twenty cases at one extreme of the curve and the twenty at the other extreme, the following observations seem of interest. The groups do

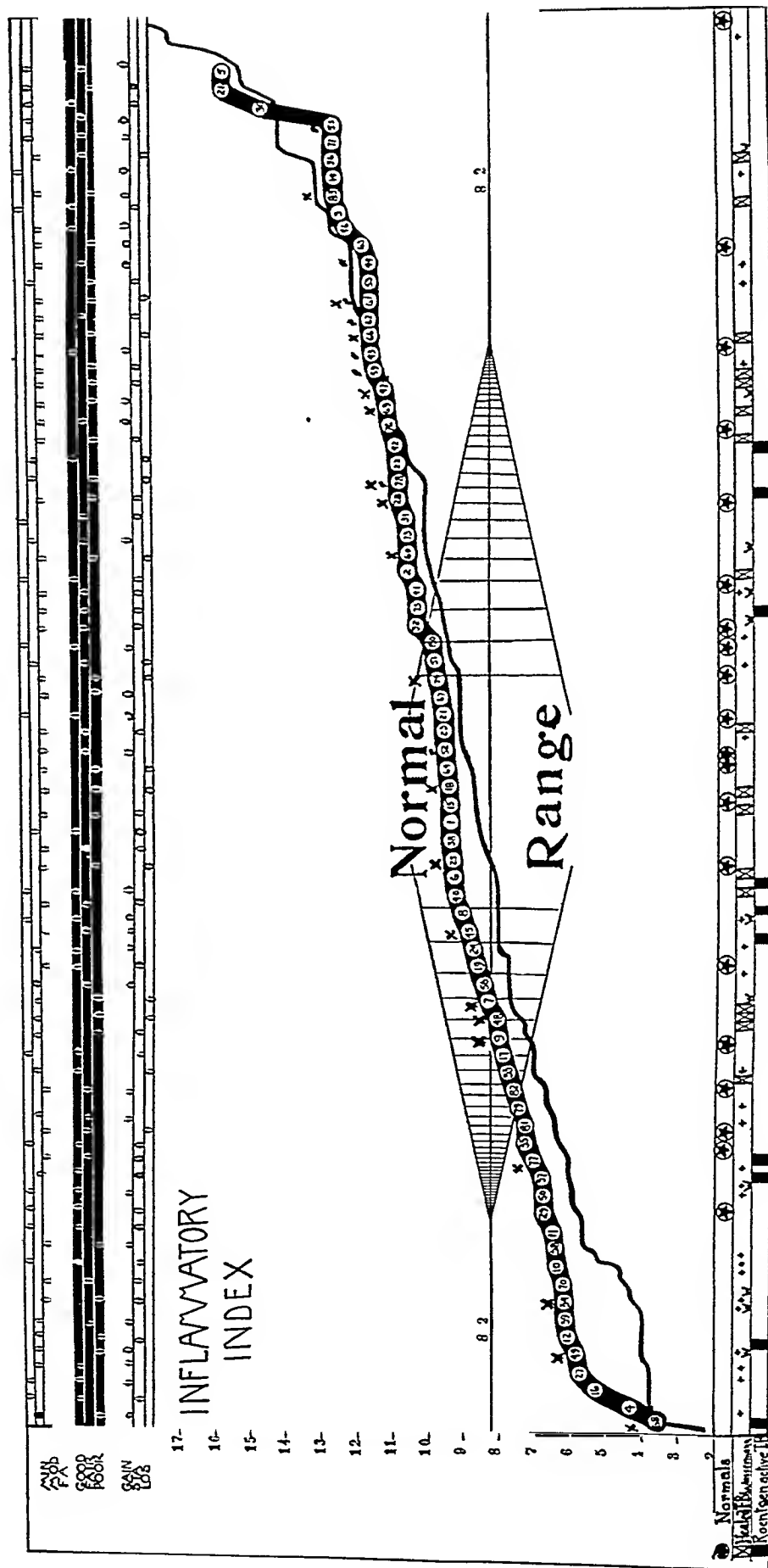


Chart 4 —The curve of the inflammatory index

TABLE 5—Comparison of the Groups with the Low, the Medium and the High Values of the Inflammatory Index, with Regard to Clinical Status

Clinical Classification of Patients	Low Index (20 Patients)	Medium Index (37 Patients)	High Index (20 Patients)
As to Type of Tuberculosis			
Minimal	35%	20%	10%
Moderately advanced	35%	30%	30%
Far advanced	30%	50%	60%
	100%	100%	100%
As to Prognosis			
Good	45%	30%	25%
Fair	30%	35%	30%
Poor	25%	35%	45%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	30%	50%
Stationary	50%	40%	35%
Losing	5%	30%	15%
	100%	100%	100%

TABLE 6—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the Inflammatory Index

Inflammatory Index	Blister Time, Hours	Capillary Permeability	Calcium, Mg per 100 Cc	Potassium, Mg	K/Ca Ratio	Globulin, per Cent of Total Protein	Protein, Mg	Age	Reaction to Epinephrine, Wheal, Mm	Reaction to Epinephrine, Flare, Mm	Endothelial Reaction	Daranyi Reaction	Deaths
63	8 85	55 69	10 6	19 6	1 85	21 8	9 113	31 6	14 02	5 69	5+ 15—	10+ 8—	6
12 33	6 25	79 9	10 8	19 22	1 78	32 7	8 72	27 6	15 02	6 84	5+ 12—	13+ 5—	6

not differ in blood chemistry, but the group with the high index has more globulin, less protein, greater intracutaneous reactivity to epinephrine and a greater number each of positive endothelial reactions and positive Daranyi reactions

CALCIUM *

The literature on the subject of the calcium and the potassium of the blood in tuberculosis is extensive. We shall refer to it but briefly.

Voorhoeve³ is of the opinion that the actual calcium balance in a tuberculous patient is of no significance, since decalcification is relative, depending on the amount of calcium supplied. In a small series of cases, he carefully studied the amount of calcium that was needed in the diet to maintain calcium balance and found no striking differences between

* Read before the Section on Pathology and Physiology at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 13, 1928

3 Voorhoeve, N. Deutsches Arch f klin Med **110** 231, 1913

tuberculous and nontuberculous subjects. The analysis of Halverson⁴ is interesting in that his determination of the calcium content of the blood of patients with advancing tuberculosis and of those convalescing from tuberculosis revealed that in persons with incipient tuberculosis (of whom those on a milk diet showed marked improvement) the value of the calcium in the serum was normal and fairly constant. In no case was the calcium value increased above the normal by a calcium diet. In patients with advanced tuberculosis the variations were greater, and patients who were improving showed, on the average, slightly higher values than did those who were not improving. No marked deviations from the normal, however, were observed in the calcium content of the serum of patients in the various stages of pulmonary tuberculosis.

A review of the literature on the therapeutic use of calcium in tuberculosis reveals a considerable body of clinical observation indicating an inhibitory effect on the tuberculosis itself, as well as on certain of its complications, a certain amount of evidence that favorable results are not obtainable, and a complete lack of convincing experimental evidence in support of calcium therapy. The hypothesis of a decalcification or demineralization in tuberculosis, according to Maver and Wells,⁵ does not receive support from the most carefully conducted investigations. There is no demonstrable deficiency of calcium in the blood or tissues in tuberculosis, and the feeding of calcium salts does not appreciably increase the amount of calcium in the blood when this is already normal. Experiments conducted by Maver and Wells showed that guinea-pigs on an ordinary laboratory diet exhibited some variations in the calcium content of the same tissue in different animals and of different tissues in the same animals, yet, averaged in a series of animals, the results were not far from identical, being generally lowest for the liver and highest for the lymph nodes, but not far from the content of the blood—that is, from 10 to 13 mg of calcium for each 100 Gm moist weight. These studies have failed to produce experimental evidence to support the empirical clinical evidence that the administration of calcium has a healing influence on the course of tuberculous infection.

Determinations of the calcium concentration of the human serum as determined by Barkus⁶ reveal a slightly increased value in the groups with destructive and destructive-proliferative tuberculosis. The values obtained in the group with proliferative disease were normal values and those in the group with atrophic manifestations of the disease were decreased.

⁴ Halverson, J. O., Mohler, H. K., and Bergeim, Olaf. *Calcium in Blood*, J. A. M. A. **68** 1309 (May 5) 1917.

⁵ Maver, M., and Wells, H. G. *Am. Rev. Tuberc.* **6** 649, 1922.

⁶ Barkus, O. *Am. Rev. Tuberc.* **9** 61, 1924.

Observations made by Matz⁷ on the blood of both normal and tuberculous subjects show that there is little variation in the calcium content of the serum. Schoenheit⁸ noted that values for calcium in the blood plasma of normal persons, determined after ashing it, were similar to the values found by others, but that those for the blood plasma of tuberculous patients were considerably less.

According to Greisheimer and Van Winkle,⁹ tuberculosis is not characterized by a demineralization. Patients who regularly drink a liberal amount of milk tend to show higher calcium levels than those who refuse it. The taking of cod liver oil does not markedly increase the calcium in the plasma of tuberculous adults even when there is clinical improvement. There is no constant difference in calcium content as between the sexes, nor is there a constant difference as between ages, although the tendency is toward lower values with increasing age. Examinations were made by Brockbank¹⁰ in seventy cases of pulmonary tuberculosis, and the value of the calcium in the serum was found varying between 8.6 and 12 mg per hundred cubic centimeters, the normal value being 10 mg per hundred cubic centimeters of serum. When the cases were graded according to their severity, it was observed that the average amount of calcium in the serum was decreased when the disease was acute, and was increased when the lesions had healed, with proportionate results in the intermediate stages. The difference amounted to 20 per cent. The calcium was not diminished in patients who were coughing up blood, as compared with patients in a similar stage of the disease but without that symptom. It was found that calcium, if given by mouth, failed to alter the level of the serum calcium materially, but when given intravenously it raised the serum content of calcium above the normal for forty-eight hours.

Nearly 100 estimations made by Ellman¹¹ show that the calcium content of the blood in pulmonary tuberculosis is within normal limits (from 9 to 11 mg per hundred cubic centimeters), but this calcium content can be raised from the minimum to the maximum with corresponding improvement in the patient's general condition by calcium or parathyroid therapy. Kromecke,¹² as well as Rosenstein and Schmidke,¹³ found an increase in the blood calcium in cases of tuberculosis with a favorable prognosis.

7 Matz, P. B. *Am Rev Tuberc* **11** 250, 1925

8 Schoenheit, E. W. *Am J M Sc* **170** 689, 1925

9 Greisheimer, E. M., and Van Winkle, C. C. *Am Rev Tuberc* **15** 270, 1927

10 Brockbank, W. *Quart J Med* **20** 431, 1927

11 Ellman, P. *Tubercle* **9** 162, 1928

12 Kromecke, Franz. *Beitr z Klin d Tuberc* **57** 467, 1924

13 Rosenstein and Schmidke. *Beitr z Klin d Tuberc* **59** 199, 1924

When our patients are grouped on the basis of the classifications of the National Tuberculosis Association, the relation of clinical status to calcium and potassium values is not clear (table 7). It will be seen that our group with minimal A disease has the highest value of the K/Ca ratio and all the more advanced cases far lower values, but there is no progression or regularity.

TABLE 7—*Comparison of the Calcium Levels and of the Potassium Levels of the Blood of Tuberculous Patients Grouped on the Basis of the Classifications of the N T A*

Group, Classified as to Tuberculosis	Calcium, Mg	Potassium, Mg	K/Ca Ratio
Minimal A	9.1	20.8	2.27
Minimal B	10.7	18.5	1.73
Moderately advanced A	10.8	17.1	1.6
Moderately advanced B	10.2	19.6	1.92
Far advanced A	9.8	19	1.93
Far advanced B	10.5	19.8	1.87
Far advanced C	10.5	18.4	1.75

TABLE 8—*Comparison of the Calcium Levels and of the Potassium Levels of the Blood of Tuberculous Patients Grouped According to the Weight Curve*

Group, Classified as to Weight Curve	Calcium, Mg	Potassium, Mg	K/Ca Ratio
Gaining	10.6	18.9	1.8
Stationary	10.4	20.1	1.96
Losing	10.2	17.7	1.73

TABLE 9—*Comparison of the Calcium Levels and Potassium Levels of the Blood of Tuberculous Patients Grouped on the Basis of Prognosis*

Group, Classified as to Prognosis	Calcium, Mg	Potassium, Mg	K/Ca Ratio
Gaining—continued to gain	10.7	18.5	1.75
Gaining—later declined	10.6	18.6	1.77
Stationary	9.1	19.8	1.97
Losing—later gained	9.8	21	2.17
Losing—continued to decline	10.2	18.1	1.79

When the patients are classified in accordance with the weight curve, the values for the groups are as recorded in table 8. Here we have a definite reduction of the calcium as we pass from the gaining to the losing group, the losing group giving the lowest value of the K/Ca ratio.

Finally, in table 9, we present the results when the grouping is made on the basis of prognosis. It is obvious that the groups who were gaining had the highest calcium levels but the high level in the last group may seem confusing. We are of the impression that the two groups present totally different pictures of calcium metabolism despite the similarity of the determinations. In the groups of patients who are gaining we have the organism maintaining a high calcium level as part of the picture of resistance, and this without loss from the body—such patients are, as a rule, in calcium balance. In the group of patients who are losing we have

a fairly high calcium level, but it represents calcium leaving the tissue and passing out from the body—these patients usually show a negative calcium balance

The three intermediate groups seem to bear out this assumption, the stationary group having the lowest amount. Certainly, the calcium values seem of greater importance than the potassium values or the values of the K/Ca ratios in all the clinical correlations.

These assumptions seem to be made more probable when we recall the calcium values of the blood of the so-called "normal" groups

TABLE 10—*Comparison of the Calcium Levels¹ and the Potassium Levels of the Blood of the "Normal" Groups*

Clinical Group	Calcium, Mg	Potassium, Mg	K/Ca Ratio
Truly normal	9.7	20.3	2.1
Having healed tuberculosis (Roentgen)	10.5	20.3	1.93
Having active tuberculosis (Roentgen)*	9.6	20.1	2.08

* Silent lesions, probably chronic

TABLE 11—*Comparison of the Groups with the Low, the Medium and the High Calcium Levels, with Regard to Clinical Status*

Clinical Classification of Patients	Low Calcium (20 Patients)	Medium Calcium (35 Patients)	High Calcium (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	20%	25%
Moderately advanced	35%	25%	45%
Far advanced	40%	55%	30%
	100%	100%	100%
As to Prognosis			
Good	40%	37%	35%
Fair	35%	20%	40%
Poor	25%	43%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	28%	55%
Stationary	35%	40%	45%
Losing	20%	32%	0
	100%	100%	100%

(table 10). Here, again, the high calcium level occurs in the healed (resistant) group, the group with only roentgen evidence of activity (chronic tuberculosis) has a low level.

We turn now to an analysis of the determinations made for the group and arranged in curves from low to high levels.

The range of calcium values for the series is from a low of 8.2 to a high of 13.4, and it is at once apparent, on inspection of chart 5, that a considerable number of the patients at the low end of the curve have died, while the patients with pleural effusion are scattered to a greater extent.

The distribution of the clinical types on the curve is shown in table 11. The most striking feature is the fact that none of the twenty patients at

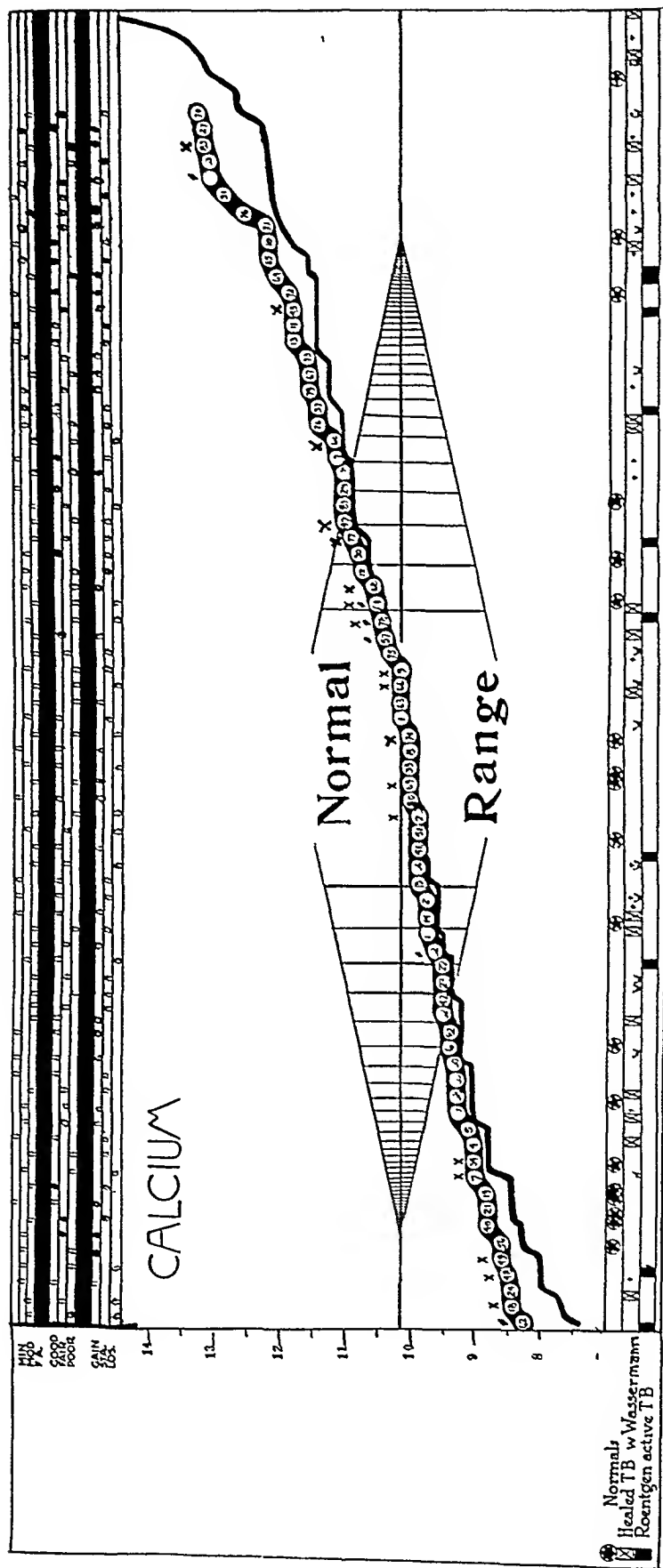


Chart 5—The calcium curve

the high end of the calcium curve were losing weight, the entire group either gaining or remaining stationary at the time of examination

In table 12, the averages for the results of the examinations of the patients with the extremely high or the extremely low calcium values are shown. The following observations seem of interest. The group with the low calcium level has, of course, a higher K/Ca ratio, the inflamma-

TABLE 12—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Calcium Levels*

Calcium, Mg per 100 Cc	Potassium, Mg	K/Ca Ratio	Blister Time, Hours	Inflammatory Index	Globulin, per Cent of Total Protein	Protein, Mg	CO ₂ Combining Power	Reaction to Thyrovin, Flare, Mm	NaCl Disappearance Time (McClure Aldrich), Min	Corpuscles/Plasma Ratio	Reaction to Epinephrine, Vagotonic	Reaction to Epinephrine, Sympathetico tonic	Deaths
8.93 12.1	19.4 19.8	2.17 1.62	8 6.9	8.46 9.5	27 34.2	8.42 9.68	55.4 57.3	3.8 2.97	89.1 65.7	41 39.6	17 12	5 8	6 5

tory index is somewhat lower because of a longer blister time, the McClure-Aldrich sodium chloride disappearance time is somewhat longer, the corpuscle/plasma ratio is a little higher and the number of "vagotonic" reactions to epinephrine is somewhat greater

POTASSIUM

When we examine the potassium curve in chart 6, the relation to deaths would indicate that these are more likely to occur in the patients with the high potassium range. The clinical distribution of the cases on the curve is shown in table 13. No clearcut influence of the potassium levels on any clinical feature tabulated is revealed. This is evident, too,

TABLE 13—*Comparison of the Groups with the Low, the Medium and the High Potassium Levels, with Regard to Clinical Status*

Clinical Classification of Patients	Low Potassium (20 Patients)	Medium Potassium (25 Patients)	High Potassium (20 Patients)
As to Type of Tuberculosis			
Minimal	20%	23%	30%
Moderately advanced	45%	28%	25%
Far advanced	35%	49%	45%
	100%	100%	100%
As to Prognosis			
Good	40%	28%	50%
Fair	30%	28%	30%
Poor	30%	44%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	51%	25%
Stationary	35%	31%	60%
Losing	25%	18%	15%
	100%	100%	100%

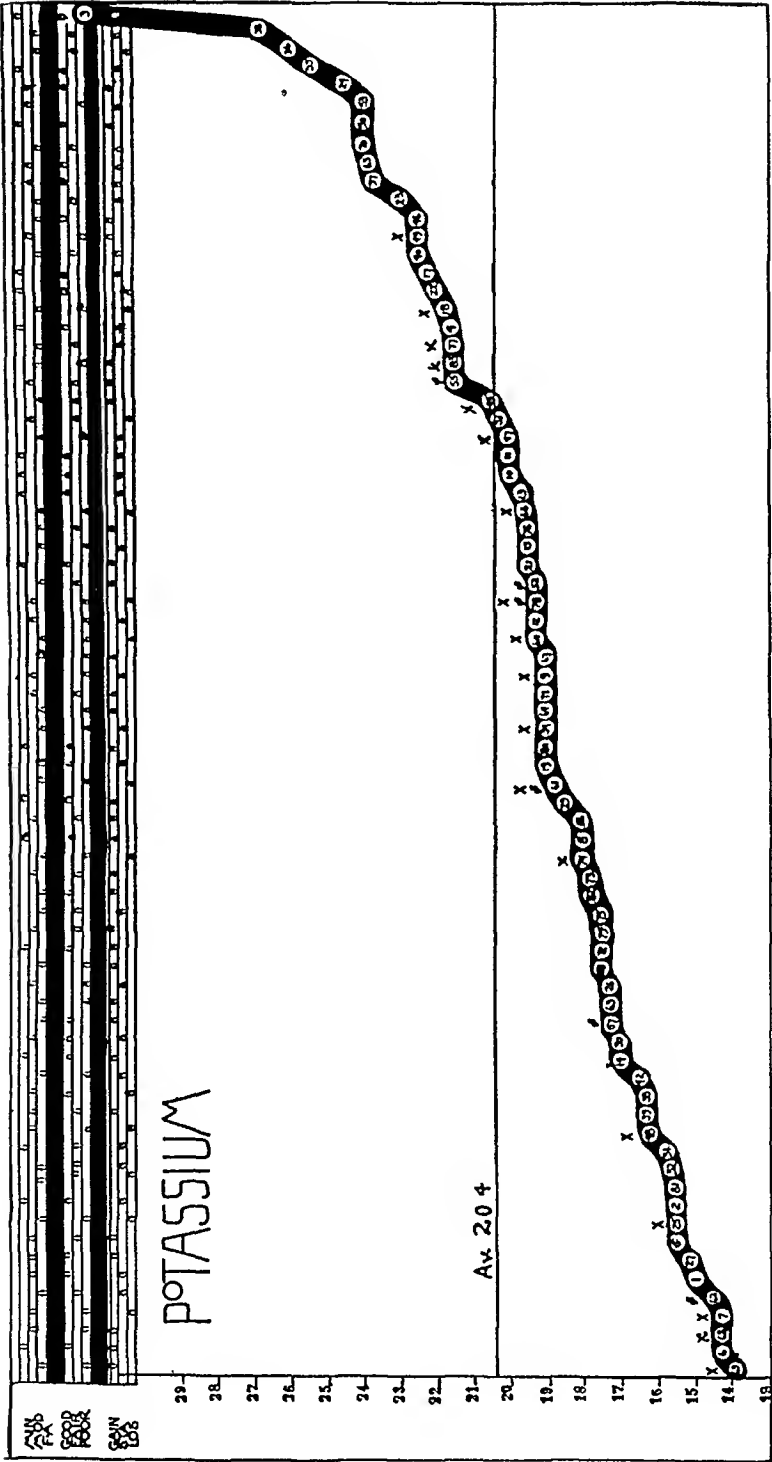


Chart 6—The potassium curve

when we inspect the averages of the other determinations for the two extreme groups (table 14) The only fact of apparent interest is the greater size of the reactions to thyroxin in the group with the low level of potassium In part 1, table 1, the relation between the reactions of the skin to thyroxin and the potassium level is made evident

TABLE 14—*Comparison of the Results of the Examinations of the Groups with the Low and the High Potassium Levels*

Potassium, Mg per 100 Cc	Calcium, Mg	K/Ca Ratio	Age	Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	Corpuscles/Plasma Ratio	Deaths
15.5	10	1.56	23.8	9.6	3.35	40.7	5
23.7	10.2	2.37	33.8	8.4	2.55	38.1	6

THE K/CA RATIO

The K/Ca ratio has apparently much less influence on the tuberculous process than the actual amount of calcium In the curve in chart 7, the deaths are well distributed along the various levels, as are the cases with pleural effusion

TABLE 15—*Comparison of the Groups with the Low, the Medium and the High Values of the K/Ca Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Ratio (20 Patients)	Medium Ratio (35 Patients)	High Ratio (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	20%	20%
Moderately advanced	45%	28%	25%
Far advanced	30%	52%	45%
	100%	100%	100%
As to Prognosis			
Good	35%	31%	50%
Fair	30%	25%	35%
Poor	35%	44%	15%
	100%	100%	100%
As to Weight Curve			
Gaining	55%	34%	35%
Stationary	30%	45%	45%
Losing	15%	23%	25%
	100%	100%	100%

The clinical status of the groups with the low, medium and high values of the K/Ca ratio is made evident in the percentages recorded in table 15 The only apparently significant feature is that with a high value of the ratio the prognosis is apparently better

The averages for various determinations in the examination of the extreme groups show no striking differences (table 16) The group

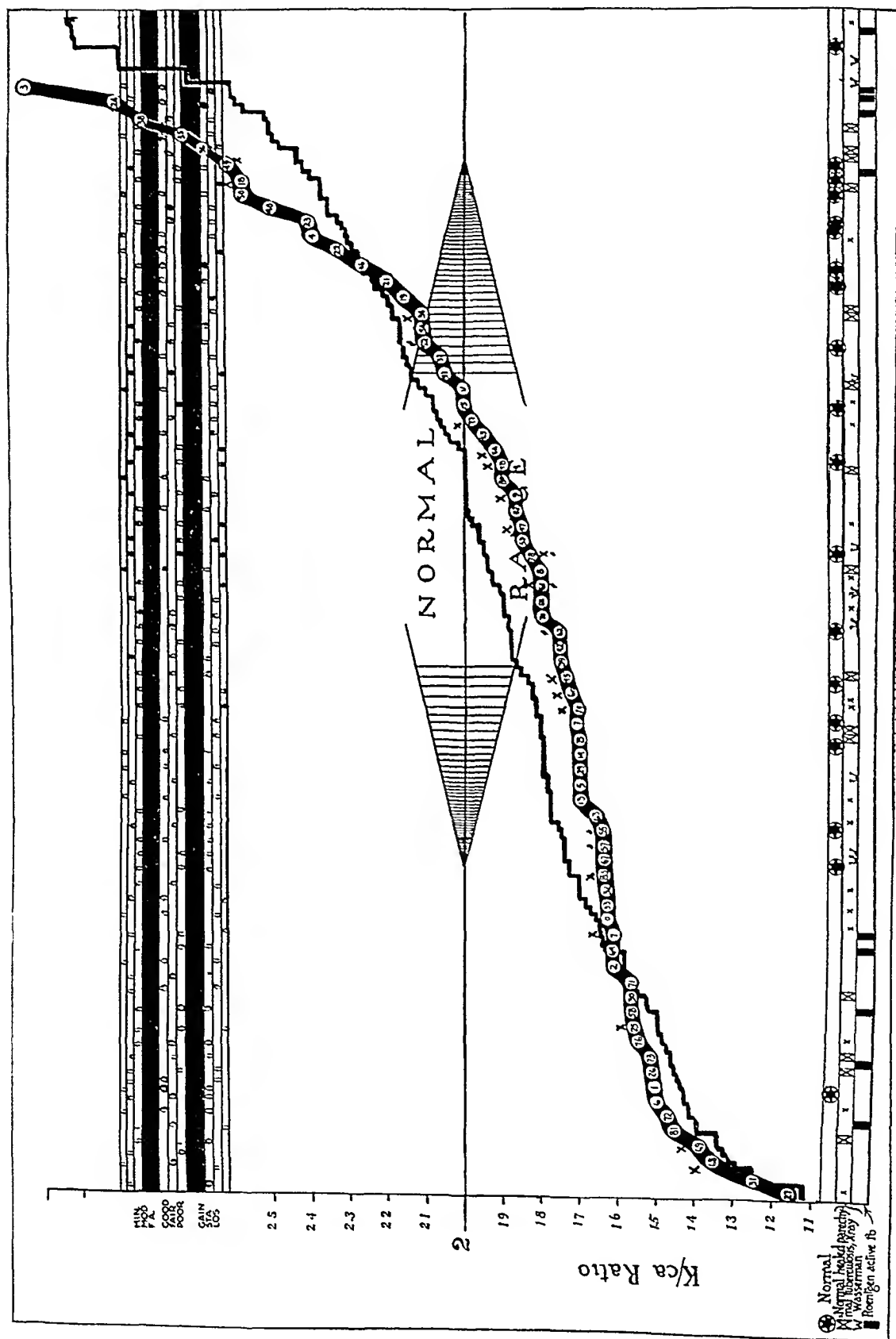


Chart 7—The curve of the K/Ca ratio

with the low value of the ratio weighs slightly less, has a slightly lower value of the cholesterol lecithin ratio, a smaller flare at the site of injection of epinephrine and a larger wheal at the site of injection of thyroxin, and the salt solution resorption time is a little shorter

TABLE 16—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the K/Ca Ratio*

K/Ca Ratio	Calcium, Mg per 100 Cc	Potassium, Mg	Inflammatory Index	Pulse Pressure	Weight/Length Ratio	Lecithin, Mg	Cholesterol/Lecithin Ratio	Reaction to Epinephrine, Flare, Mm	Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	NaCl Resorption (McClure Aldrich) Time, Minutes	Corpuscles/Plasma Ratio	Deaths
1.49	11.1	16.5	9.3	45.6	1.91	173.5	1.16	6.16	9.65	2.4	71.6	38.1	6
2.41	9.29	22.6	8.79	51.4	2.06	156	1.26	7.56	8.3	3.85	84.7	40	4

PROTEIN

The average percentage of the protein in the blood serum of the "normal" group was determined as 8. For the serum of our tuberculous group, this was 8.8, and, as one surveys chart 8, it appears that patients with more advanced tuberculosis have a higher concentration. Thus, there appear to be more deaths in this region of the curve and also more cases with pleural effusion.

TABLE 17—*Comparison of the Groups with the Low, the Medium and the High Levels of Protein in the Serum, with Regard to Clinical Status*

Clinical Classification of Patients	Low Protein (20 Patients)	Medium Protein (41 Patients)	High Protein (20 Patients)
As to Type of Tuberculosis			
Minimal	35%	22%	10%
Moderately advanced	40%	26%	25%
Far advanced	25%	52%	65%
	100%	100%	100%
As to Prognosis			
Good	60%	36%	15%
Fair	30%	26%	40%
Poor	10%	38%	45%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	34%	55%
Stationary	40%	53%	15%
Losing	15%	13%	30%
	100%	100%	100%

The percentage distribution of the patients with the low and the high concentrations of protein on the basis of clinical status is given in table 17. It appears that more cases of far advanced tuberculosis occur at the upper end, at which also, the prognosis is poorest. Curiously,

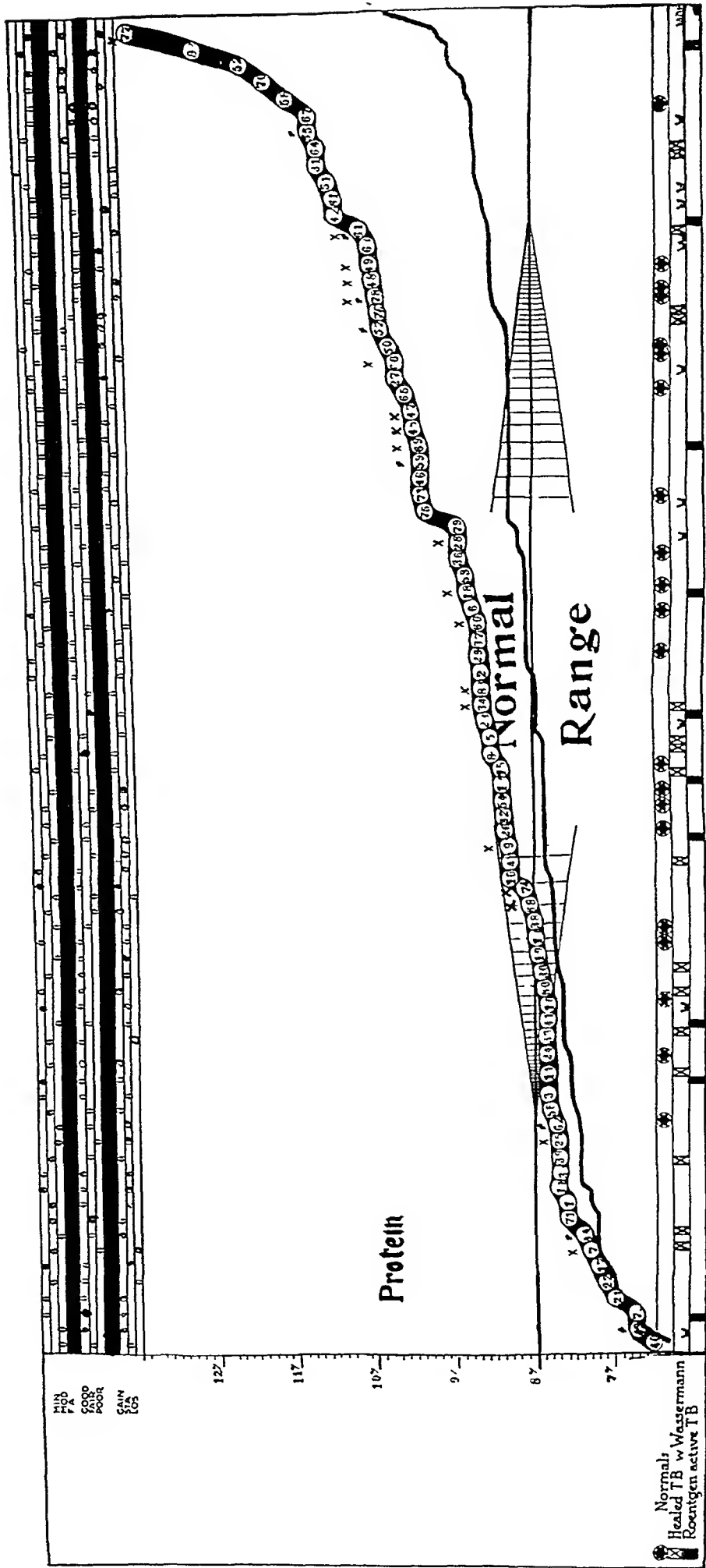


Chart 8—The protein curve

both gain and loss in weight are most marked here, reflecting, probably, the fact that in many instances these gains represent fluctuations in the water balance

Table 18, presenting the results of the examinations of the two extreme groups, offers a number of contrasts, some of which are contradictory. The group with the low protein has less globulin, fewer positive tuberculin and Daranyi reactions, a higher value of the corpuscles/plasma ratio, a greater number of sympatheticotonic vascular reactions, a longer blister time, but a somewhat higher permeability, and a higher value of the K/Ca ratio.

TABLE 18—*Comparison of the Results of the Examinations of the Groups Having the Lowest and the Highest Concentrations of Protein in the Serum*

Protein, Mg per 100 Gc	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Albumin	Globulin, per Cent of Total Protein	Reaction to Tuberculin, Mm	Daranyi Reaction	Corpuscles/Plasma Ratio	Reaction to Epinephrine	Deaths
7.454	7.6	70.5	9.5	9.79	19.4	2	77.2	22.8	9+	11+	40.7	9V 11S	2
10.526	6.8	61.9	9.07	10.71	19	1.77	60.2	39.8	14+	16+	37.7	13V 7S	7

GLOBULINS

There can be little doubt concerning the relation of the increase in globulins to the prognosis in tuberculosis. With this increase in the globulins in cases of far advanced tuberculosis, are to be associated the changes in the sedimentation time, the increase in fibrinogen, the various flocculations, which depend on the colloidal instability, etc.

When we examine the curve in chart 9, it is immediately apparent that the high end has the majority of deaths. The cases showing pleural exudations are equally distributed.

The percentage analysis of the cases plotted on the curve with regard to clinical condition is shown in table 19. The majority of the cases of far advanced tuberculosis occur at the high end and the prognosis here is poorest. On the other hand, the relation of gain or loss of weight to the curve is uncertain. While, of course, in the low end of the curve a majority of the patients are gaining or are stationary, in the high end the gaining, the stationary and the losing are about equally divided. As mentioned in the corresponding discussion of the total protein, this is probably to be explained on the basis of the fluctuation of the water balance, which occurs so readily in these cases of far advanced tuberculosis.

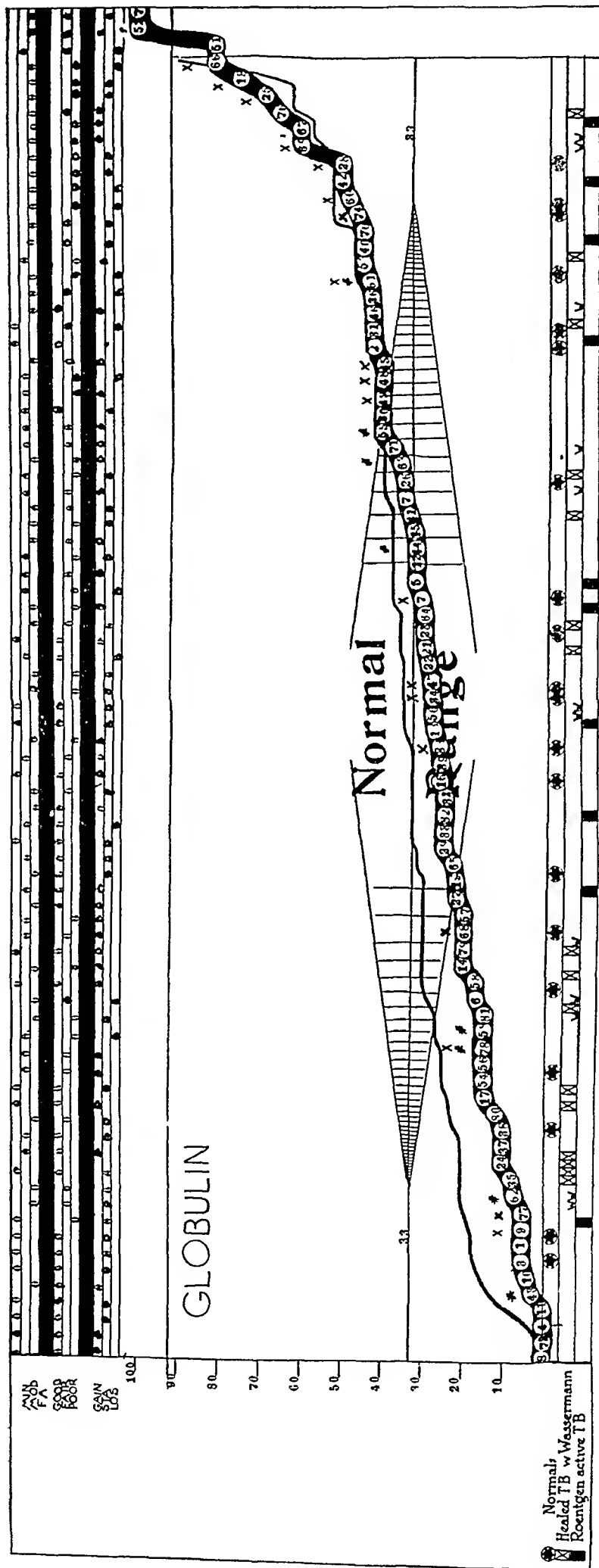


Chart 9—The globulin curve

Table 20, in which the two extreme groups are compared, shows the following conditions, many of which correspond with the observations in the groups having the high and the low values of total protein. The group with the low globulins has a longer blister time, a lower inflammatory index, a higher value of the K/Ca ratio, less protein, a higher value of the corpuscles/plasma ratio, fewer positive tuberculin and Daranyi reactions and a greater number of vagotonic reactions to epinephrine.

TABLE 19—*Comparison of the Groups with the Low, the Medium and the High Levels of Globulins, with Regard to Clinical Status*

Clinical Classification of Patients	Low Globulins (20 Patients)	Medium Globulins (42 Patients)	High Globulins (20 Patients)
As to Type of Tuberculosis			
Minimal	55%	19%	5%
Moderately advanced	25%	40%	10%
Far advanced	20%	41%	85%
	100%	100%	100%
As to Prognosis			
Good	65%	38%	5%
Fair	25%	28%	40%
Poor	10%	34%	55%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	50%	30%
Stationary	60%	38%	35%
Losing	5%	12%	35%
	100%	100%	100%

TABLE 20—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Concentrations of Globulins in the Serum*

Globulins, Mg per 100 Cg	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Albumin	Protein, Mg	Tuberculous Complement Fixation	Daranyi Reaction	Corpuscles/Plasma Ratio	Diagnosis	Reaction to Epinephrine	Deaths
7.2	7.9	65.8	8.6	10.1	20.7	2.07	92.8	8.18	15+ Neg 6+	12+ Neg 8+	4.16	9 minimal 7 mod ad 4 far ad	13V 7S	3
59.8	6.62	68.1	10.3	10.5	19.6	1.88	40.7	9.37	3- Neg 17+	1- Neg 18+	39.1	1 minimal 2 mod ad 17 far ad	6V 14S	10

BASAL METABOLIC RATE

The basal metabolic rate for the tuberculous group averages +6.5, and the curve (chart 10) proportionately follows that established for our "normal" and miscellaneous clinical group. The fatal cases and the majority of those with pleural effusion are grouped at the upper end of the curve. The clinical status of each of the groups with the low, the medium and the high rates is shown in the percentages listed in table 21.

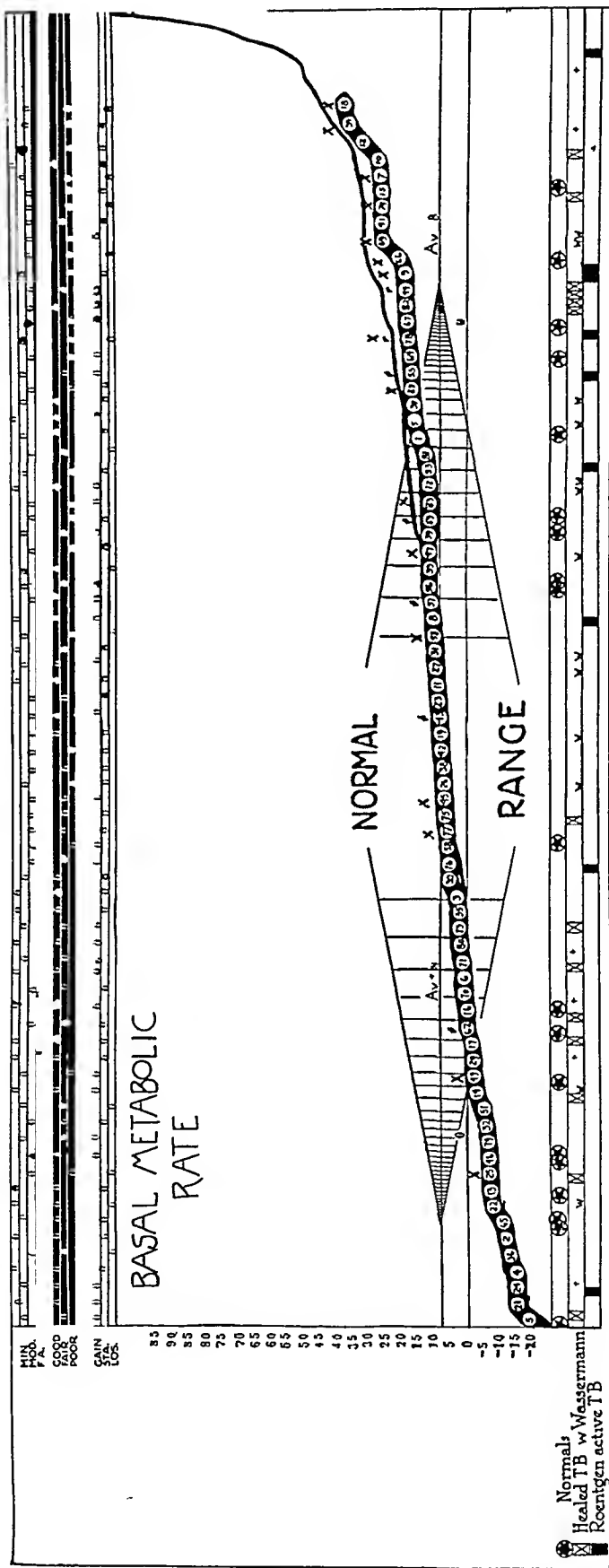


Chart 10—The curve of the basal metabolic rate

In the group with the low basal metabolic rate, the cases of minimal manifestation predominate, in the group with the high basal metabolic rate, the cases of far advanced tuberculosis. The same ratios are true for the good and the poor prognoses. There is no apparent relation to the weight curve.

In table 22, in which the groups at the ends of the curve are compared in detail, the group with the high rate is shown to have a some-

TABLE 21—*Comparison of the Groups Having, Respectively, Low, Medium and High Basal Metabolic Rates, with Regard to Clinical Status*

Clinical Classification of Patients	Low Basal Metabolic Rate (20 Patients)	Medium Basal Metabolic Rate (35 Patients)	High Basal Metabolic Rate (20 Patients)
As to Type of Tuberculosis			
Minimal	45%	23%	10%
Moderately advanced	30%	31%	30%
Far advanced	25%	46%	60%
	100%	100%	100%
As to Prognosis			
Good	60%	40%	20%
Fair	30%	37%	15%
Poor	10%	23%	65%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	48%	35%
Stationary	40%	48%	40%
Losing	20%	9%	25%
	100%	100%	100%

TABLE 22—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Basal Metabolic Rates*

Basal Metabolic Rate	Calcium, Mg per 100 Cc	Potassium, Mg	K/Ca Ratio	Kromayer Light Erythema Time, Min	CO ₂ Combining Power	Ice Reaction Time, Seconds	Reaction to Epinephrine, Wheal, Mm	Reaction to Epinephrine, Flare, Mm	Diagnosis	Prognosis	NaOI Solution Resorption Time, Minutes	Deaths
- 8.6	9.8	19.6	2	95.9	55.7	13.3	14.36	6.21	8 minimal 7 mod advanced 5 far advanced	12 good 6 fair 2 poor	80.8	3
+21.3	10.3	19.3	1.87	71	57.2	9.3	16.37	6.93	2 minimal 6 mod advanced 12 far advanced	4 good 3 fair 13 poor	69	11

what lower value of the K/Ca ratio, a shorter Kromayer light erythema time and a shorter ice reaction time and a larger flare on the injection of epinephrine.

VASCULAR REACTIONS TO EPINEPHRINE

In two papers previously published,¹⁴ we described the reactions of our tuberculous group to the subcutaneous injection of epinephrine.

14 Petersen, W. F., and Levinson, S. A. *Am Rev Tuberc* 18:616, 1928.
Hillebrand and De Trana. *Ibid* 18:626, 1928.

Both the individual curves and their analysis on the basis of clinical status, as well as composite curves, were presented in detail

CO₂ COMBINING POWER

We might expect that the CO₂ combining power of the patient would show relatively little concurrence with the clinical activity. In chart 11,

TABLE 23—*Comparison of the Groups with the Low, the Medium and the High CO₂ Combining Power, with Regard to Clinical Status*

Clinical Classification of Patients	Low CO ₂ Combining Power (20 Patients)	Medium CO ₂ Combining Power (39 Patients)	High CO ₂ Combining Power (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	25%	5%
Moderately advanced	10%	36%	45%
Far advanced	60%	39%	50%
	100%	100%	100%
As to Prognosis			
Good	40%	41%	20%
Fair	30%	25%	40%
Poor	30%	34%	40%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	44%	45%
Stationary	45%	38%	30%
Losing	20%	18%	25%
	100%	100%	100%

TABLE 24—*Comparison of the Results of the Examinations of the Groups Having the Lowest and the Highest CO₂ Combining Power*

CO ₂ Combining Power	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Kromayer Light Erythema Time, Min	Ice Reaction Time, Seconds	Reaction to Epinephrine, Flare, Min	Reaction to Thyroxin, Flare, Min	Corpuscles/Plasma Ratio	Daranyi Reaction	Deaths
49.16	10.3	18.9	1.84	103	13.6	6.24	1.32	40.75	11+ 7-	5
63.18	10.26	17.9	1.74	83.1	9.4	7.17	3.4	38.2	18+	5

our strictly normal material is scattered over the entire range of the normal curve, while the cases in which there is roentgen evidence of active tuberculosis tend toward the upper end. The curve for our tuberculous material indicates that deaths, as well as pleural effusion are scattered.

The general clinical status of the patients represented on the curve also indicates that there is no significant difference clinically between the extremes (table 23).

Table 24, in which the groups with the extremely high and the extremely low CO₂ combining power are compared, shows the following

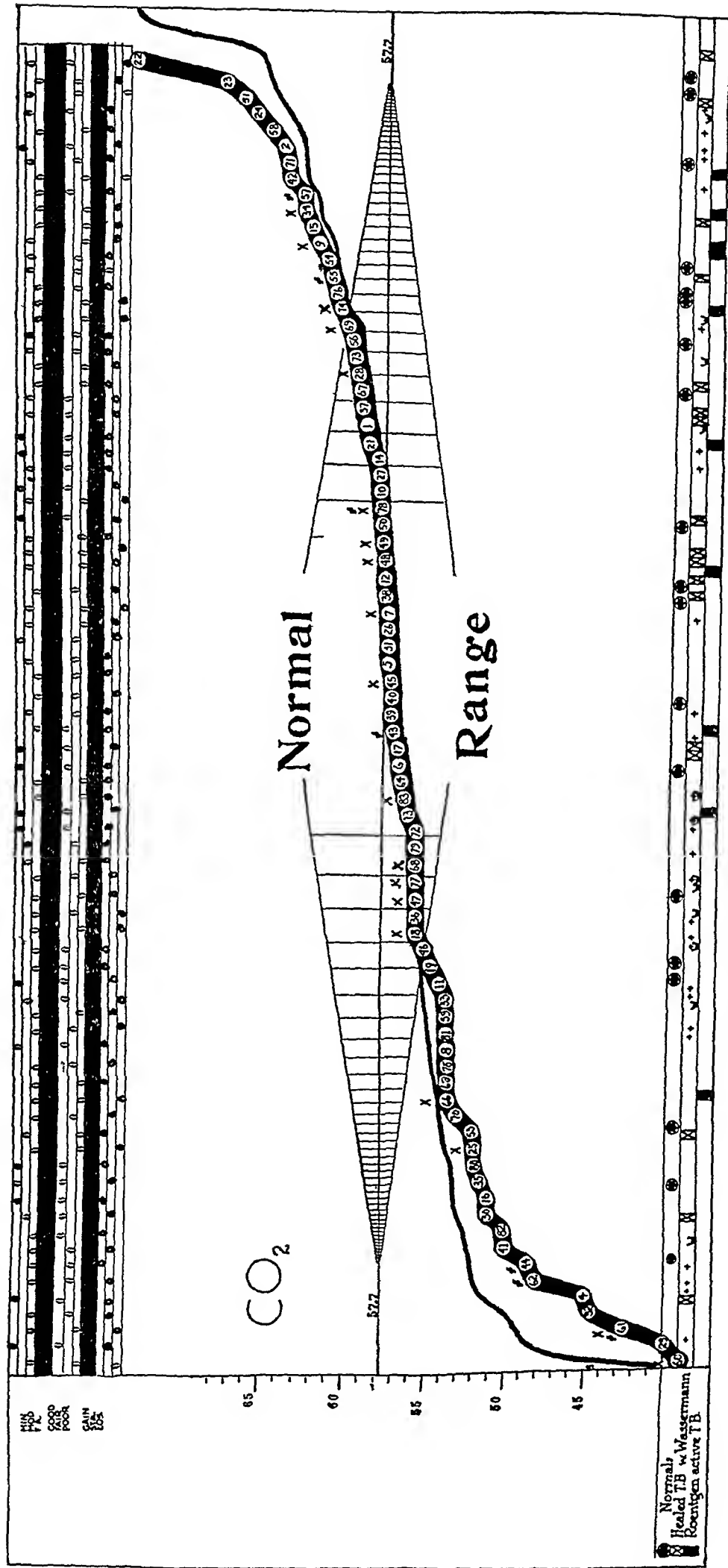


Chart 11—The curve of the CO₂ combining power

differences between the groups. The group with the low CO_2 combining power has a higher level of potassium and a higher value of the K/Ca ratio, a longer Kromayer light erythema time, a longer ice reaction time, a smaller flare at the site of the intracutaneous injection of epinephrine and thyroxin and fewer positive Daranyi reactions.

CHOLESTEROL

The association of high cholesterol values with more favorable types of tuberculous infection has been repeatedly suggested. In chart 12, our values for the series of tuberculous patients are considerably lower than those for the "normal" persons and persons with miscellaneous clinical conditions. If it is permissible to draw conclusions from the limited material, it appears, too, that the cases of healed tuberculosis among our "normal" and miscellaneous groups are more apt to be associated with high cholesterol values.

TABLE 25—Comparison of the Groups with the Low, the Medium and the High Cholesterol Content in the Blood, with Regard to Clinical Status

Clinical Classification of Patients	Low Cholesterol (20 Patients)	Medium Cholesterol (38 Patients)	High Cholesterol (20 Patients)
As to Type of Tuberculosis			
Minimal	15%	23%	20%
Moderately advanced	15%	37%	40%
Far advanced	70%	40%	40%
	100%	100%	100%
As to Prognosis			
Good	30%	37%	35%
Fair	20%	30%	45%
Poor	50%	33%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	30%	44%	45%
Stationary	50%	37%	45%
Losing	20%	19%	10%
	100%	100%	100%

TABLE 26—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of Cholesterol in the Serum

Cholesterol, Mg per 100 Cc	Diagnosis	Blood Pressure	Globulin, per Cent	Protein, Mg	Reaction to Epinephrine, Wheal, Mm	Reaction to Tuberculin, Mm	Daranyi Reaction	Deaths
157.7	3 minimal 3 moderately advanced 14 far advanced	109.1	39.2	8.365	15.37	8.6	15+ 1—	10
235.1	4 minimal 8 moderately advanced 8 far advanced	123.7	30.9	8.953	14.41	11.1	12+ 5—	3

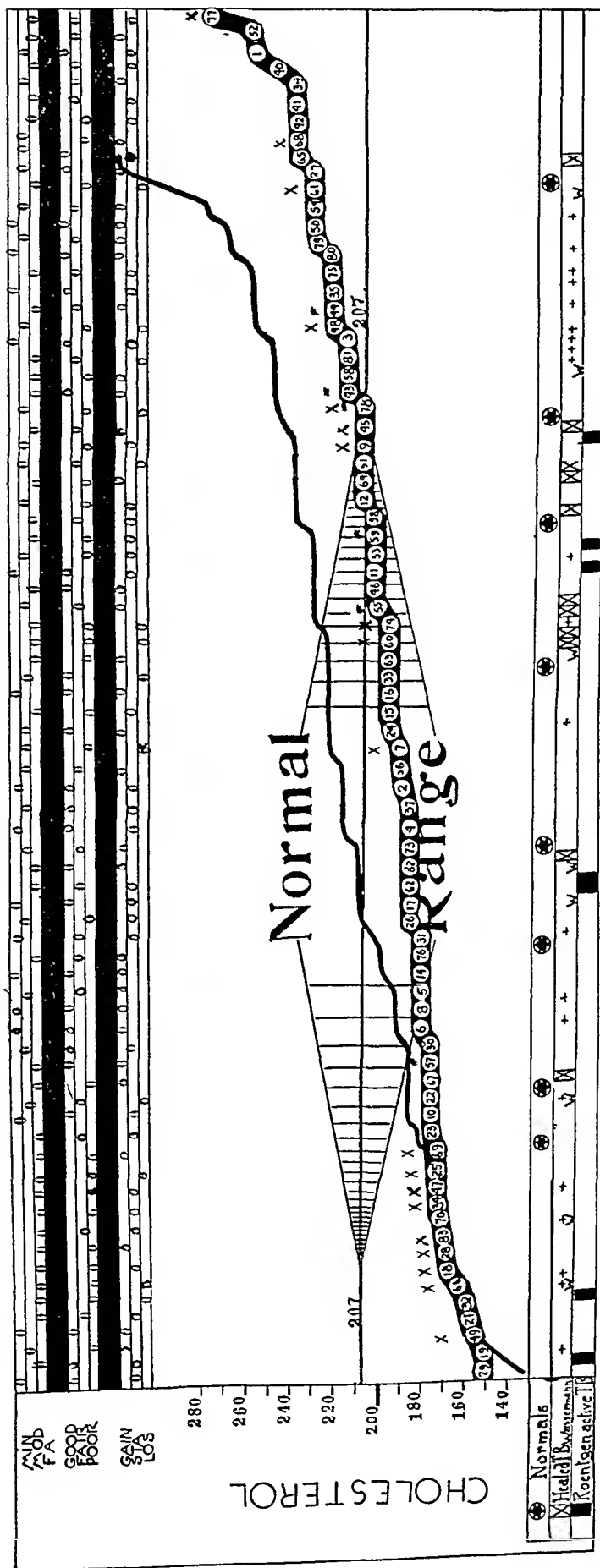


Chart 12 —The cholesterol curve

It is rather striking that so many fatal cases are at the lower end of the curve, the cases with effusion appear more frequently at the opposite end

The clinical status of the groups with the low, the medium and the high cholesterol values is shown in the percentages set forth in table 25. The group with the lowest cholesterol values contains more cases of far advanced tuberculosis with poor prognosis, many of the patients in this group, however, are either stationary or gaining in weight. The group with the highest cholesterol values contains a greater number of cases of moderately or far advanced tuberculosis, the majority of the patients in this group have a fair or good prognosis and are either stationary or gaining in weight.

Table 25, in which the twenty patients at the low end of the curve are compared with the twenty at the high end, indicates that the low group has a lower blood pressure, more globulin and a smaller reaction to tuberculin. The low group also is characterized by ten fatal cases, as compared with three in the high group.

LECITHIN

An analysis of the lecithin curve in chart 13 from the point of view of the clinical status of the patients represented in it reveals a clinical distribution as tabulated in table 27. The group at the low end of the curve shows the cases of far advanced tuberculosis to be in the majority, with poor or, at best, fair prognosis. The high group, on the other hand, shows more cases of minimal tuberculosis and more with a good prognosis. The relation of these groups to the weight curve is uncertain.

TABLE 27—*Comparison of the Groups with the Low, the Medium and the High Lecithin Values, with Regard to Clinical Status*

Clinical Classification of Patients	Low Lecithin (20 Patients)	Medium Lecithin (36 Patients)	High Lecithin (20 Patients)
As to Type of Tuberculosis			
Minimal	10%	20%	40%
Moderately advanced	35%	27%	30%
Far advanced	55%	53%	30%
	<hr/> 100%	<hr/> 100%	<hr/> 100%
As to Prognosis			
Good	15%	38%	55%
Fair	40%	30%	15%
Poor	45%	32%	30%
	<hr/> 100%	<hr/> 100%	<hr/> 100%
As to Weight Curve			
Gaining	40%	50%	25%
Stationary	40%	33%	60%
Losing	20%	17%	15%
	<hr/> 100%	<hr/> 100%	<hr/> 100%

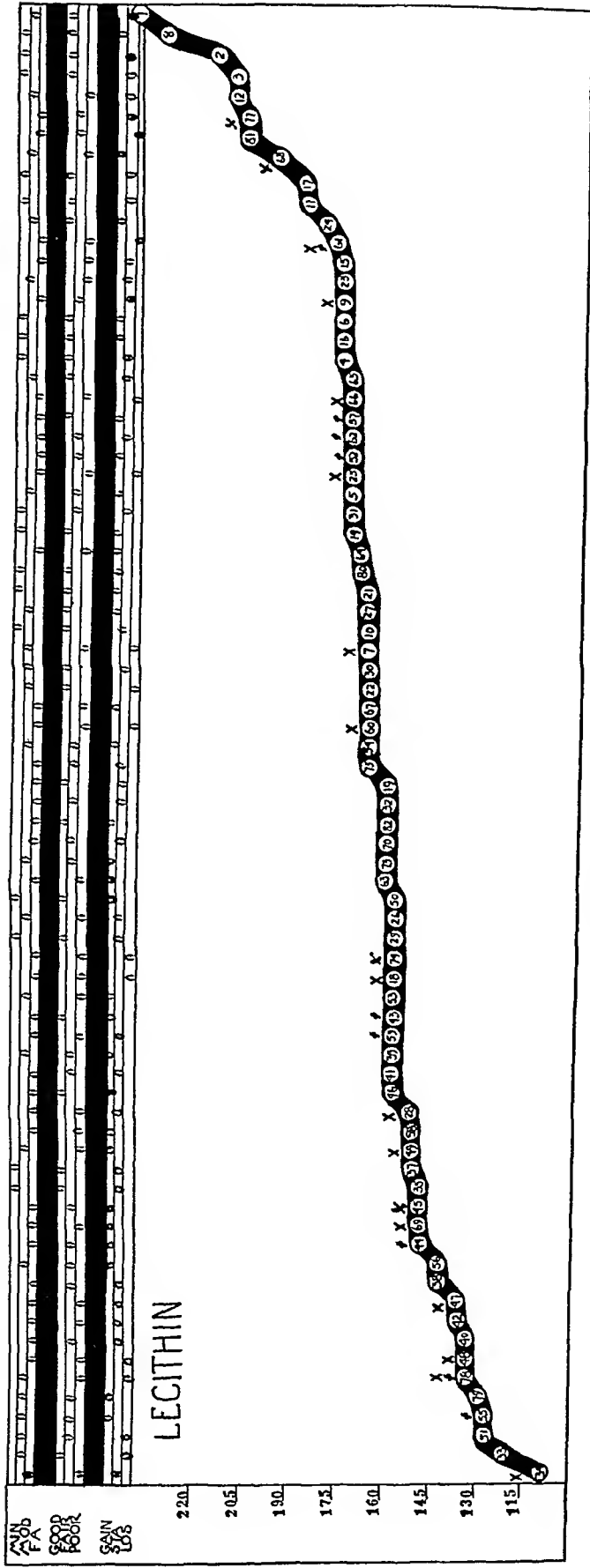


Chart 13 —The lecithin curve

The table in which the groups at the extreme ends of the curve are compared (table 28) shows the following. The low group has a shorter blister time, higher globulin, a longer Kromayer light erythema time, a larger flare at the site of the injection of epinephrine, as well as a larger reaction to thyroxin and a greater number of positive tuberculin and Daranyi reactions.

TABLE 28—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Lecithin Values of the Serum*

Lecithin, Mg per 100 Ce	Cholesterol/Lecithin Ratio	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Ca Ratio	Globulin, per Cent of Total Protein	Protein, Mg	Kromayer Light Erythema Time, Min	Reaction to Epinephrine, Wheal, Mm	Reaction to Epinephrine, Flare, Mm	Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	Weight/Length Ratio	Reaction to Tuberculin, Flare, Mm	Daranyi Reaction	Deaths
138	146	7.21	64.4	8.96	10	19.3	1.94	32.6	9.049	84	15.07	7.91	9.45	5.57	1.9	14+ 7-	14+ 4-	8
191	1084	8.5	67.1	8.2	10.2	19.3	1.95	24	8.75	67.8	15	5.46	8.3	1.8	1.92	7+ 12-	11+ 8-	6

CHOLESTEROL/LECITHIN RATIO

Since high cholesterol and low lecithin values presumably have some prognostic significance, we have studied this ratio as it involves our material. It is apparent from a survey of the curve in chart 14 that deaths are scattered over the entire range. Here again, cases with effusion are seemingly more common with the high values.

The relation of the ratio to the clinical status of the patient as indicated in table 29 is not clear. There are more cases of moderately advanced and far advanced tuberculosis at the high end of the curve,

TABLE 29—*Comparison of the Groups with the Lowest and the Highest Values of the Cholesterol/Lecithin Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Value (20 Patients)	Medium Value (36 Patients)	High Value (20 Patients)
As to Type of Tuberculosis			
Minimal	45%	14%	10%
Moderately advanced	15%	40%	40%
Far advanced	40%	46%	50%
	100%	100%	100%
As to Prognosis			
Good	60%	33%	20%
Fair	15%	22%	55%
Poor	25%	45%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	35%	50%
Stationary	55%	44%	30%
Losing	10%	21%	20%
	100%	100%	100%

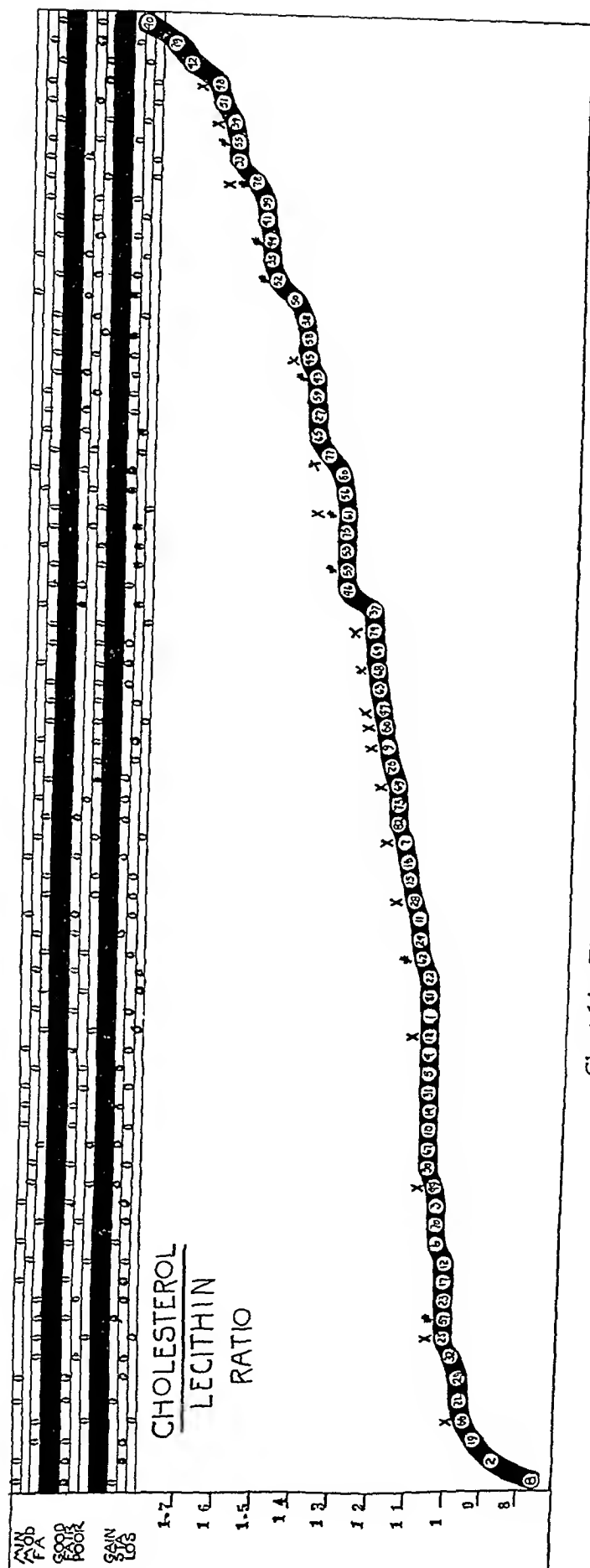


Chart 14 —The curve of the cholesterol/lecithin ratio

the majority of the patients with the high values are gaining and have a fair prognosis. On the other hand, in the low group there are more cases of minimal manifestation of the disease. The group has more patients with good prognosis (60 per cent) and a far greater number (90 per cent) who are either gaining or stationary. It is evident that the index is of prognostic value only when we take into consideration the stage of the tuberculous process.

As there are no apparent correlations with the results of the other tests, the tables have been omitted. It may be recalled that determinations of cholesterol in our group of 100 "normal" men showed few correlations with other determinations (table 1, part 1).

NONSPECIFIC LEUKOCYTIC REACTION TO AOLAN

When a bland protein is intracutaneously injected, a peripheral vascular constriction takes place, with a coincident leukopenia. At the same time, a splanchnic dilatation apparently occurs and the leukocytes accumulate for the time being in the internal organs. The degree of the shift in the leukocyte count is of value in estimating the autonomic status. Muller¹⁵ studied the reaction in detail.

We studied such reactions in the series of patients with tuberculosis. The results of the composite curves have been published elsewhere.¹⁶

CORPUSCLE/PLASMA RATIO

The corpuscle/plasma ratio has been described as of definite prognostic value in tuberculosis. Chart 15 reveals that both deaths and cases of pleural effusion are uniformly distributed.

The distribution of the clinical activity with regard to the low, medium and high values of this ratio is shown in table 30. The group

TABLE 30—*Comparison of the Groups with the Low, the Medium and the High Values of the Corpuscles/Plasma Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Value (20 Patients)	Medium Value (40 Patients)	High Value (20 Patients)
As to Type of Tuberculosis			
Minimal	20%	22.5%	25%
Moderately advanced	10%	40%	35%
Far advanced	70%	37.5%	40%
	100%	100%	100%
As to Prognosis			
Good	40%	40%	30%
Fair	20%	25%	45%
Poor	40%	35%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	40%	40%
Stationary	35%	45%	45%
Losing	20%	15%	15%
	100%	100%	100%

¹⁵ Muller, E. F. *Munchen med Wchnschr* 70 1113, 1923.

¹⁶ Petersen, W. F., and Levinson, S. *Am Rev Tuberc* 18 839, 1928.

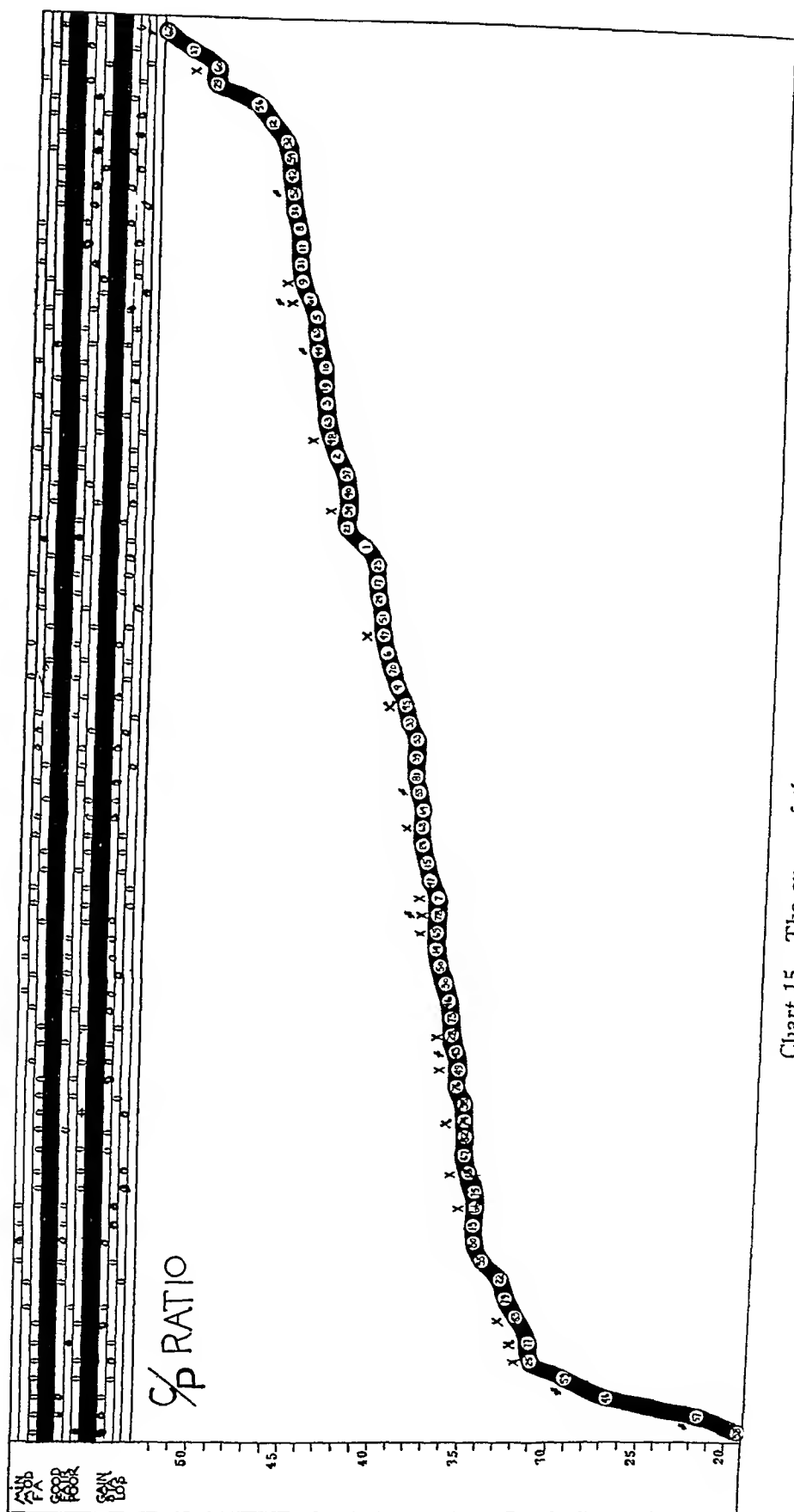


Chart 15—The curve of the corpuscles/plasma ratio

at the low end of the curve shows proportionately more cases of far advanced tuberculosis with poor prognosis. There is no relation to the weight curve.

TABLE 31—Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the Corpuscles/Plasma Ratio

Corpuscles/Plasma Ratio	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg per 100 Cc	Potassium, Mg	K/Ca Ratio	Protein, Mg	CO ₂ Combining Power	Weight/Length Ratio	Deaths
31.76	6.94	63.4	0	10.47	19.05	1.9	9.25	56.92	1.79	6
47.42	7.66	68.1	0.48	10.53	18.51	1.75	8.77	53.14	2.05	5

When we examine table 31, in which the group at the extreme ends of the curve are compared, we observe that the K/Ca ratio is higher in the low group, as are the serum protein and the CO₂ combining power and that, as a group, these patients with the low value of the ratio in question weigh considerably less.

ICE REACTION TIME

For our group of 100 "normal" men the ice reaction time averaged 19 seconds while for our group of twenty actually normal persons it was reduced to 14.5 seconds. This group with the low reaction time had an average age of 40 years. The group with tuberculosis with an average age of 31 years should show an ice reaction time below 14.5 seconds, and we actually found it to be 12 seconds.

The curve (chart 16) indicates that both deaths and cases with pleural effusion are more common in the patients with a short ice reaction time. On the other hand the cases in which there was roentgenologic evidence of active tuberculosis in our "normal" series appear more frequently with longer ice reaction time (age?).

The clinical status of the groups represented on the ice reaction curve is shown in table 32. It seems that in the low and middle regions of the curve there are more cases of far advanced tuberculosis while the prognosis and the weight curve appear to be somewhat better in the region of the delayed ice reaction.

Table 33 in which the groups at the extreme ends of the curve are compared in detail also indicates that the persons with a delayed reaction have a more favorable outlook. The group with the short reaction time

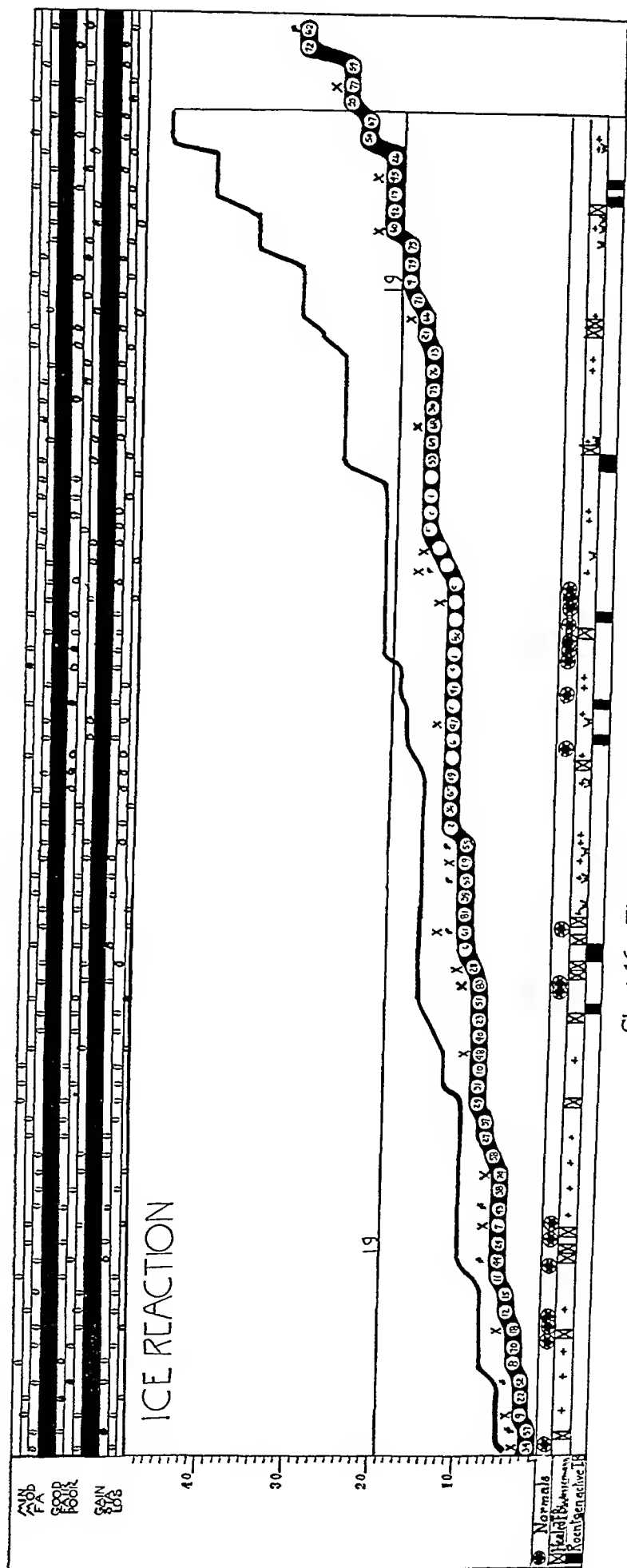


Chart 16—The curve of the ice reaction time

has many more cases with complications. The Kromayer light erythema time is shorter, the CO_2 combining power is higher, the wheal at the site of the injection of epinephrine is somewhat larger and the reaction to tuberculin less intense.

TABLE 32—*Comparison of the Groups with the Short, the Medium and the Long Ice Reaction Time, with Regard to Clinical Status*

Clinical Classification of Patients	Short Time (20 Patients)	Medium Time (42 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal	10%	21%	35%
Moderately advanced	35%	30%	20%
Far advanced	55%	49%	45%
	100%	100%	100%
As to Prognosis			
Good	40%	35%	35%
Fair	20%	31%	40%
Poor	40%	34%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	43%	45%
Stationary	40%	38%	45%
Losing	20%	19%	10%
	100%	100%	100%

TABLE 33—*Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Time for the Reaction to Ice*

Ice Reaction Time, Seconds	Blister Time, Hours	Calcium, Mg per 100 Cc	Potassium, M/L	K/Oa Ratio	Kromayer Light Ery- thema Time, Min	CO_2 Combining Power	Age	Reaction to Epineph- rine, Wheal, Mm	Endothelial Reaction	Reaction to Tubercu- lin, Mm	Deaths
4	7.7	10.2	19.9	1.95	70	59.2	35.12	15.77	6+ 14-	7.1	8
20.7	7.2	10.6	19.5	1.84	98.6	55.42	31.8	14.42	9+ 11-	9.3	5

KROMAYER LIGHT REACTION TIME

The reactive erythema following upon the application of the Kromayer light appears somewhat more rapidly in tuberculous persons, as is evident in chart 17. While the time averages 120 minutes for our "normal" group, it is only 90 minutes for the patients with tuberculosis.

The clinical distribution is shown in table 34. The table shows clearly that it is impossible to correlate the reaction with any particular clinical phase.

Table 35, in which the groups at the extreme ends of the curve are compared in detail, also illustrates the relative similarity of the two groups and it is for this reason that we have included the averages. The

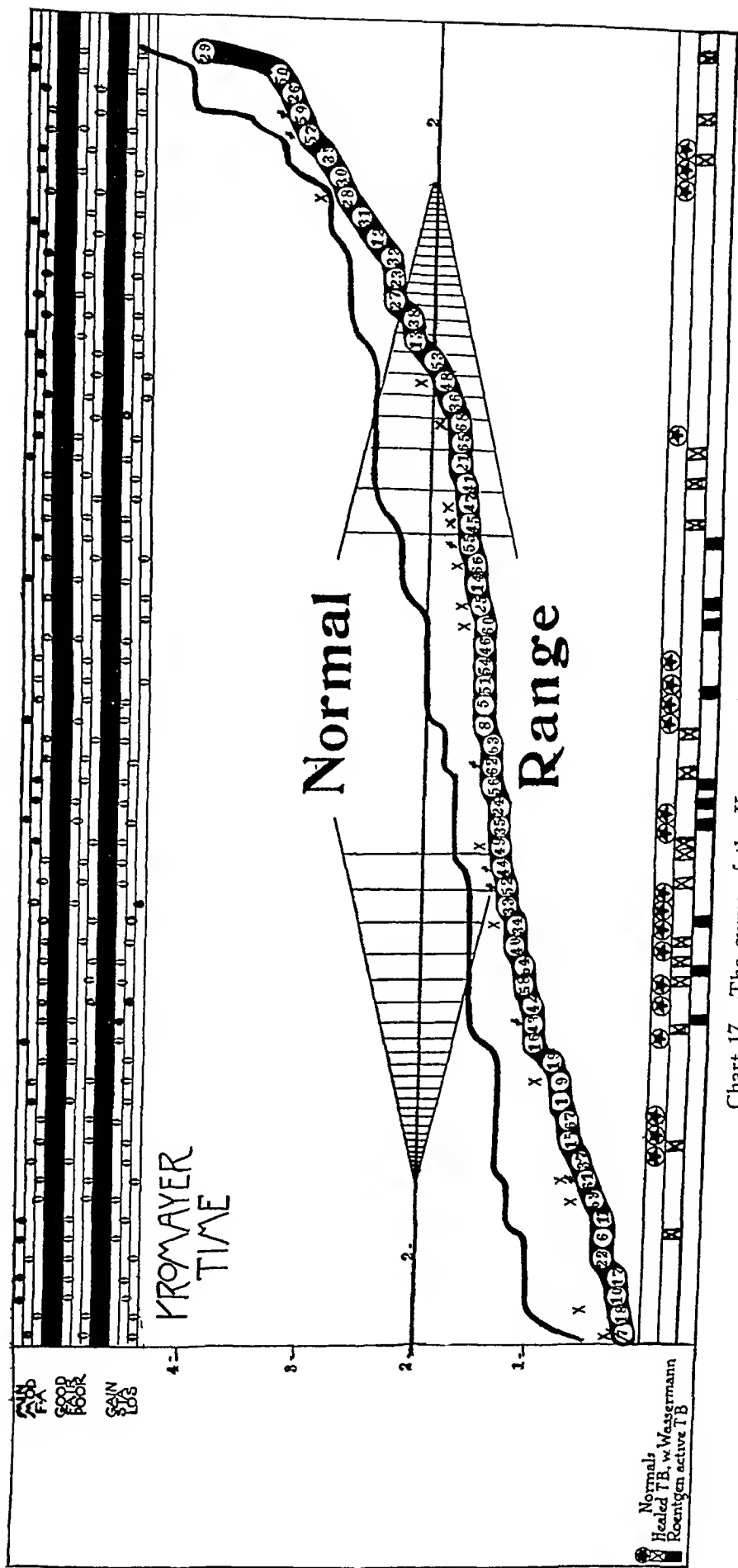


Chart 17 —The curve of the Kromayer light erythema time

only striking difference lies in the endothelial reaction—the group with the short reaction time gives 50 per cent positive reactions as compared with 10 per cent for the group with the delayed reaction. This is confirmed when we examine the Kromayer reaction time of all the patients with the positive Rumpel-Leede endothelial reaction. It is then found to be 65 minutes as contrasted with 105 minutes for the cases in which the Rumpel-Leede endothelial reaction is negative.

TABLE 34—*Comparison of the Groups with the Short, the Medium and the Long Time for the Appearance of Kromayer Light Erythema, with Regard to Clinical Status*

Clinical Classification of Patients	Short Time (20 Patients)	Medium Time (25 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	16%	20%
Moderately advanced	25%	32%	45%
Far advanced	50%	52%	35%
	100%	100%	100%
As to Prognosis			
Good	50%	28%	35%
Fair	0	44%	30%
Poor	50%	28%	35%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	56%	25%
Stationary	45%	28%	65%
Losing	30%	16%	10%
	100%	100%	100%

TABLE 35—*Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Time for the Appearance of the Kromayer Light Erythema*

Kromayer Light Erythema Time, Min	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Reaction to Epinephrine, Wheal, Mm	Reaction to Epinephrine, Flare, Mm	Reaction to Morphine, Wheal, Mm	Reaction to Morphine, Flare, Mm	Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	Endothelial Reaction	Deaths
35.8	7.62	65.8	8.8	16.57	7.2	7.4	5.1	7.35	3.72	10+	6
133.1	7.6	67.8	9.3	15.26	6.25	6.92	4.15	8.82	3.12	10— 2+ 18—	6

MC CLURE-ALDRICH TEST

The disappearance time of intracutaneously injected salt solution, as suggested by McClure-Aldrich, seems of considerable interest in tuberculosis. Chart 18 shows that in our tuberculous patients this time varied from 15 to 190 minutes. Deaths occur more frequently in the low part of the curve, pleural effusion is more common at the high end.

The clinical status of the cases as classified on the curve is recorded in table 36. In general, the distribution of minimal, moderately advanced and far advanced tuberculosis is practically equal, the prognosis is somewhat better in the cases with delayed absorption and the weight curve is decidedly more favorable at the upper end of the curve.

TABLE 36—Comparison of the Groups with the Short, the Medium and the Long Resorption Time for Salt Solution, with Regard to Clinical Status

Clinical Classification of Patients	McClure-Aldrich Salt Solution Disappearance Test		
	Short Time (20 Patients)	Medium Time (39 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	25%	15%
Moderately advanced	25%	28%	35%
Far advanced	50%	47%	50%
	100%	100%	100%
As to Prognosis			
Good	30%	36%	40%
Fair	20%	30%	40%
Poor	50%	34%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	30%	38%	65%
Stationary	35%	48%	20%
Losing	35%	14%	15%
	100%	100%	100%

TABLE 37—Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Disappearance Time for Salt Solution (McClure-Aldrich Test)

NaCl Disappearance Time (McClure-Aldrich Test)	Capillary Permeability	Inflammatory Index	Calcium, Mg	Potassium, Mg	K/Oa Ratio	Kromayer Light Erythema Time, Min	Ice Reaction, Seconds	Reaction to Epinephrine, Wheal, Mm	Reaction to Epinephrine, Flare, Mm	Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	Reaction to Tuberculin, Mm	Deaths
42.4	70.4	9.99	10.48	19.5	1.86	79.7	8.75	15.7	5.98	8.3	2.67	5.5	3
117.3	65.46	8.86	9.8	19.25	1.95	102.7	11.8	13.66	7.53	9.6	2.95	10.4	3

When we compare the groups at the extreme ends of the curve (table 37), the following points seem of interest. There are no apparent differences in the amount of globulin, in the group with the short time, the protein is 8.5 per cent as compared with 9 per cent for the group with the delayed disappearance. The group with the short time has greater permeability of the capillaries, a higher inflammatory index, more calcium, and much shorter Kromayer and ice reaction times. The wheal at the site of the injection of epinephrine is larger, but the flare is smaller, as is also the thyroxin wheal and the reaction to tuberculin.

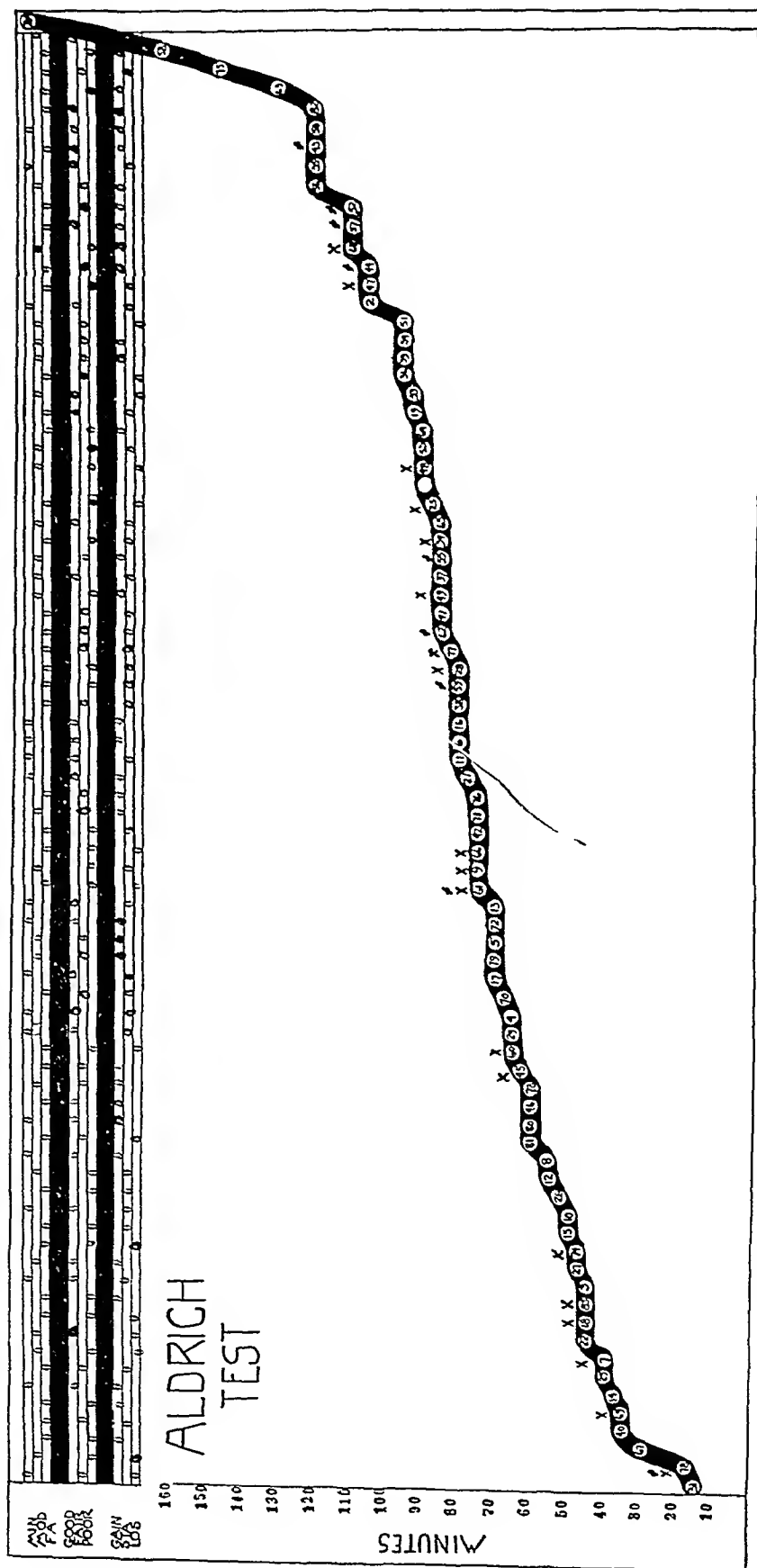


Chart 18—The curve of the disappearance time of the salt solution in the McClure-Aldrich test

Feldman ¹⁷ studied some thirty patients ill with terminal tuberculosis and found that the shortest absorption times were in the patients with the most toxic condition

RUMPEL-LEEDE ENDOTHELIAL REACTION

Thirty-two of the eighty-three patients gave a positive endothelial reaction. These patients were proportionately distributed among the groups with minimal, moderately advanced and far advanced tuberculosis. There may be some significance in the fact that only one of the patients with the positive reaction had a pleural effusion, that one third of them gave a primary sympatheticotonic reaction and that their average Kromayer light erythema time was shortened to 65 minutes. (The average for the group with tuberculosis was 90 minutes.)

INTRACUTANEOUS REACTION TO EPINEPHRINE WHEEL

The average size of the wheal at the site of the injection of epinephrine in our "normal" series was 19.2 mm. In the tuberculous group, it averaged 15.2. From the curve in chart 19, it may be noted

TABLE 38—Comparison of the Groups with the Smallest, the Medium and the Largest Diameters of the Wheal at the Site of the Injection of Epinephrine, with Regard to Clinical Status

Clinical Classification of Patients	Small Wheal (20 Patients)	Medium Wheal (42 Patients)	Large Wheal (20 Patients)
As to Type of Tuberculosis			
Minimal	0	33%	20%
Moderately advanced	55%	23%	23%
Far advanced	45%	44%	55%
	100%	100%	100%
As to Prognosis			
Good	10%	46%	40%
Fair	50%	21%	30%
Poor	40%	33%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	46%	35%
Stationary	40%	31%	60%
Losing	25%	23%	5%
	100%	100%	100%

that more deaths occurred in the patients with small wheals, while cases with pleural effusion were scattered over the entire range. The clinical status of the groups with the small, the medium and the large wheals is shown in table 38. There are no cases of minimal manifestation in the group with the small wheals, and the group has either a fair or a poor prognosis. In the group with the large wheals, the prognosis seems better and more of the cases are at least stationary. The group with the most favorable prognosis seems to be that in which the wheal is intermediate

17 Feldman, A. Intradermal Salt Solution Test in Tuberculosis, Arch. Int. Med. 41: 549 (April) 1928.

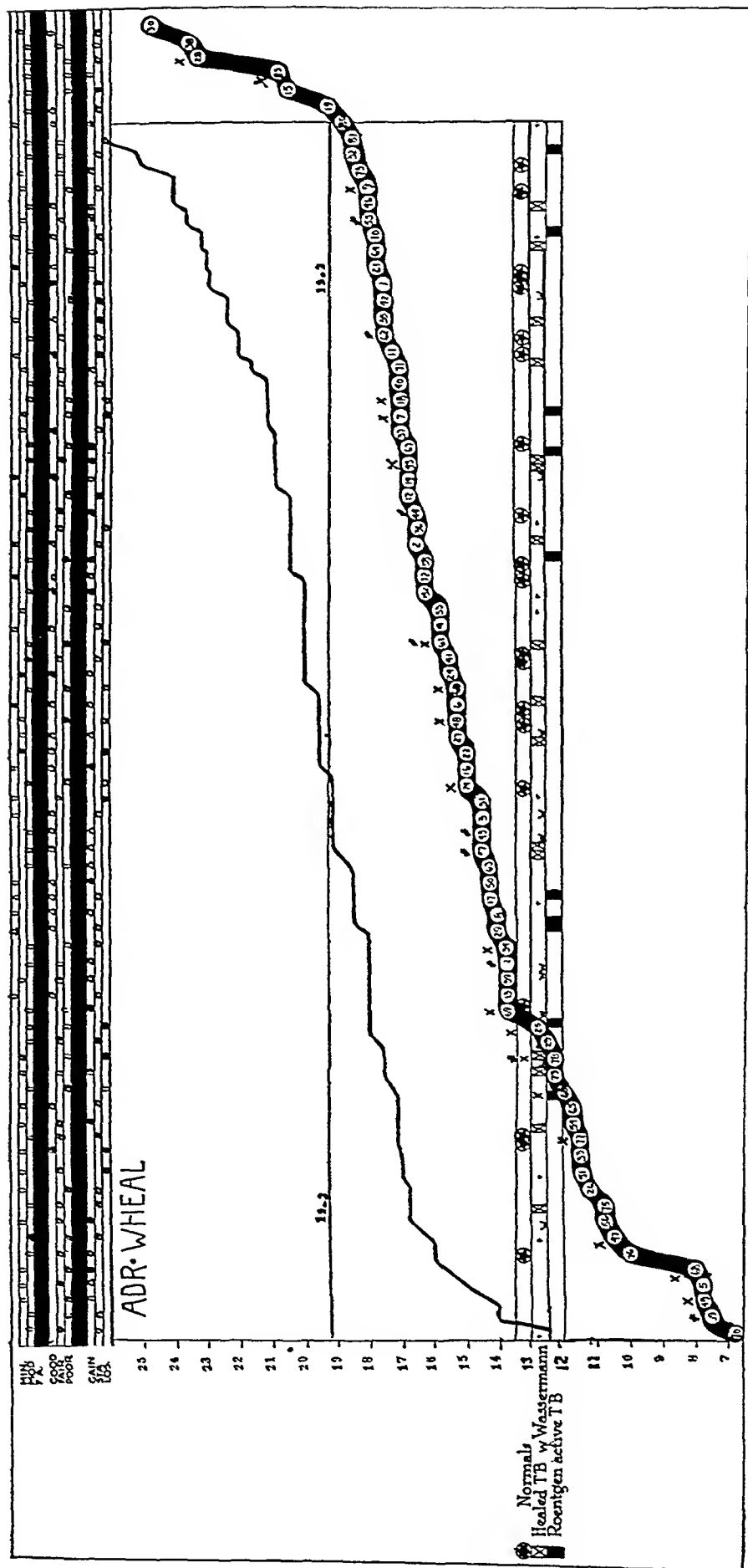


Chart 19—The curve of the intracutaneous reaction to epinephrine (wheal)

The analysis of the results in the tests of the groups at the ends of the curve (table 39) indicates that the flare of the reaction to epinephrine and capillary permeability are somewhat greater in the group with large wheals, and the same observation holds true for the reaction to tuberculin. The absorption time for sodium chloride solution in this group is somewhat less.

TABLE 39—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Wheal at the Site of the Injection of Epinephrine*

Reaction to Epinephrine, Wheal, Mm	Reaction to Epinephrine, Flare, Mm	Capillary Permeability	Kromayer Light Erythema Time, Min	Age	NaCl Resorption Time, Minutes	Reaction to Tuberculin, Mm	Deaths
10.47	6.32	63.6	110	29.6	82.5	9.2	8
19.22	7.844	67.6	85.8	34.5	69.1	11.9	4

INTRACUTANEOUS REACTION TO EPINEPHRINE FLARE

In our group of "normal" men, the average flare of the reaction to epinephrine had a radius of 8.8 mm. In the patients with tuberculosis, it had a radius of 6.8 mm. As with the wheal, the curve (chart 20)

TABLE 40—*Comparison of the Groups with the Small, the Medium and the Large Radii of the Flare at the Site of the Injection of Epinephrine, with Regard to Clinical Status*

Clinical Classification of Patients	Small Flare (20 Patients)	Medium Flare (42 Patients)	Large Flare (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	23%	15%
Moderately advanced	30%	31%	40%
Far advanced	45%	46%	45%
	100%	100%	100%
As to Prognosis			
Good	35%	35%	40%
Fair	30%	26%	40%
Poor	35%	39%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	38%	55%
Stationary	50%	42%	30%
Losing	10%	20%	15%
	100%	100%	100%

shows the deaths occurring in larger number in the group with the smaller flares. The clinical status of the groups with the small and the large flares is shown in table 40. There appears to be no significant relation of the size of the flare to the clinical classification, the prognosis or the weight curve, many more deaths are found in the group with the small flares.

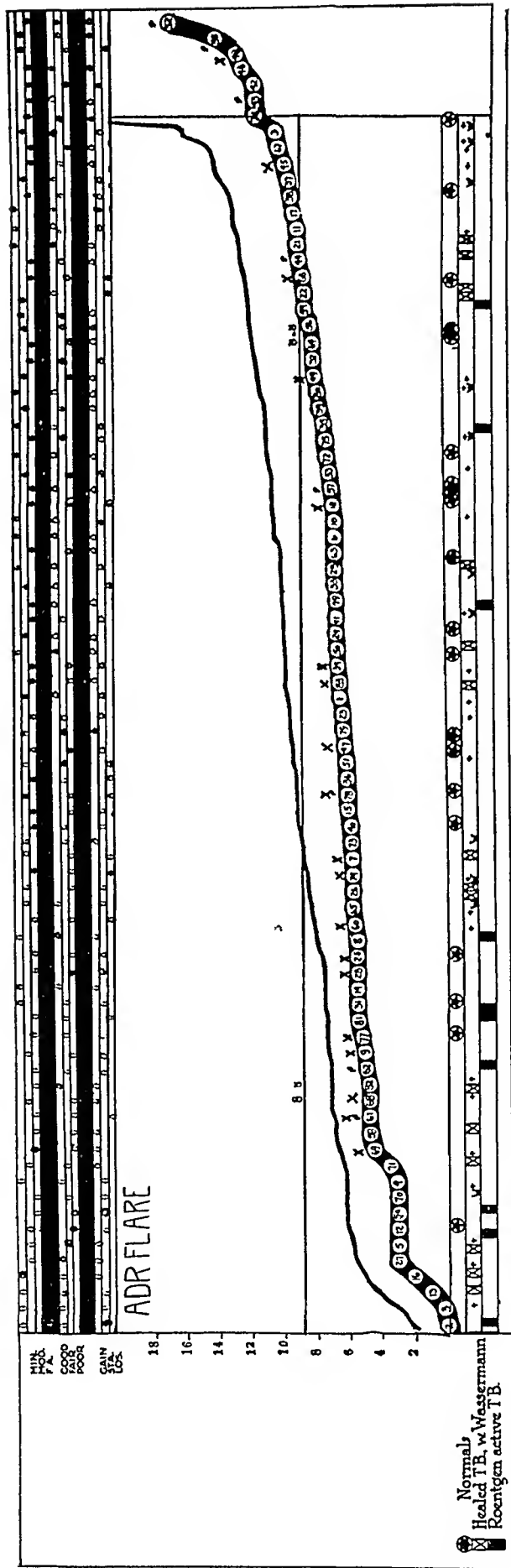


Chart 20 —The curve of the intracutaneous reaction to epinephrine (flare)

When we examine table 41, in which the group at the ends of the curve are compared in detail, we note that with the smaller flare the wheal at the site of the injection of epinephrine is somewhat smaller, and also the flare at the site of the injection of thyroxin. The blister time is somewhat longer and the capillary permeability relatively diminished so that the inflammatory index is smaller. The absorption of the sodium chloride solution is also somewhat quicker. The value of the K/Ca ratio is lower.

TABLE 41—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Radn of the Flare at the Site of the Injection of Epinephrine*

Reaction to Epineph- rine, Flare, Mm	Reaction to Epineph- rine, Wheal, Mm	Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	Blister Time, Hours	Capillary Perme- ability	Inflammatory Index	Calcium, Mg	Potassium, Mm	K/Ca Ratio	Kromayer Light Ery- thema Time, Mm	CO ₂ Combining Power	NaCl Resorption Time, Minutes	Deaths
3.691	13.82	9.35	3.25	8	62.5	8.6	10.7	18.55	1.75	95.8	54.9	73.6	9
10.56	15.8	8.75	6.3	7.1	69.3	10	10.4	20.2	1.96	77.8	58.1	81.2	2

INTRACUTANEOUS REACTION TO THYROXIN WHEEL

There seems to be no characteristic relation of the mortality nor any relation of the cases with pleural effusion to the size of the wheal at the site of the injection of thyroxin. When we examine the clinical status of the patients as grouped in the curve (chart 21), it would seem that

TABLE 42—*Comparison of the Groups with the Small, the Medium and the Large Diameters of the Wheal at the Site of Injection of Thyroxin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (20 Patients)	Medium Wheal (42 Patients)	Large Wheal (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	28%	0
Moderately advanced	25%	30%	35%
Far advanced	45%	42%	65%
	100%	100%	100%
As to Prognosis			
Good	50%	45%	5%
Fair	25%	28%	45%
Poor	25%	26%	50%
	100%	100%	100%
As to Weight Curve			
Gaining	25%	45%	55%
Stationary	55%	42%	20%
Losing	30%	13%	25%
	100%	100%	100%

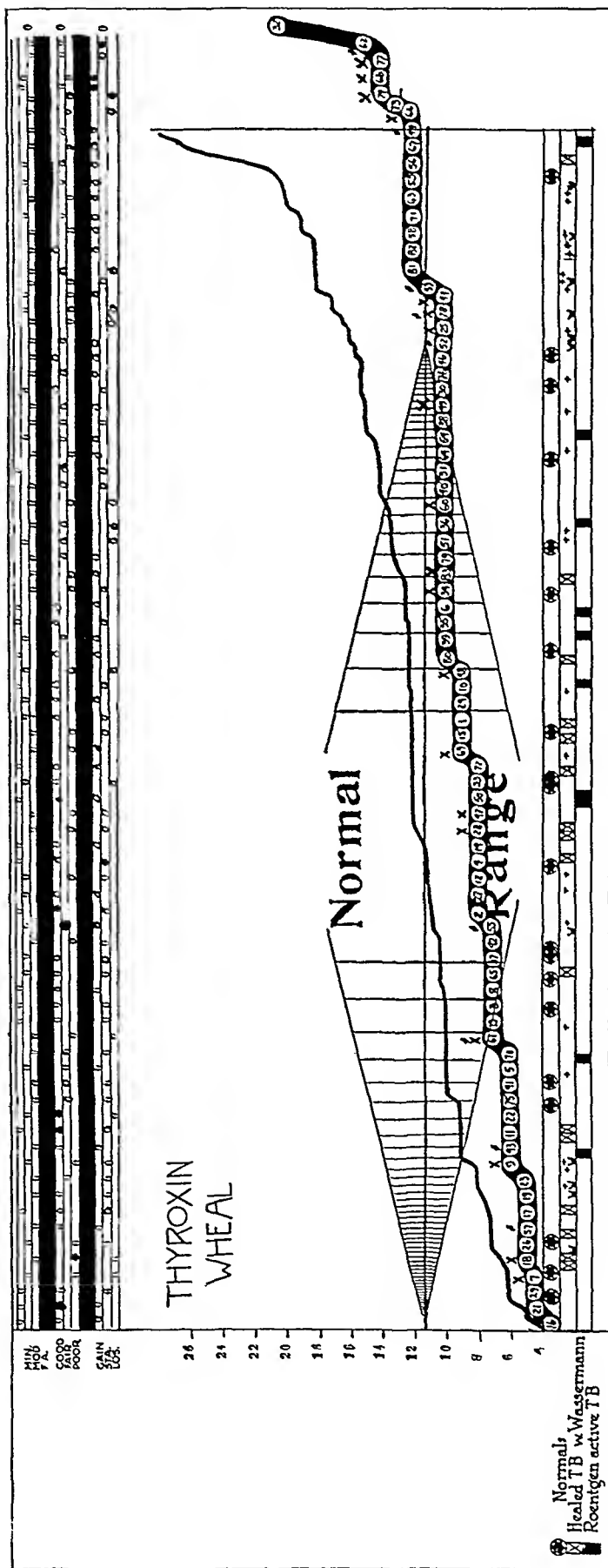


Chart 21—The curve of the intracutaneous reaction to thyroxin (wheal)

there are more cases of far advanced tuberculosis in the group with the larger wheals, that the prognosis is best in the group with the small wheals , and that the gain in weight seems to be most favorable in the groups at the intermediate and upper portions of the curve

When we examine table 43, in which the groups at the extreme ends of the curve are compared in detail, we note that the flare at the site of the injection of thyroxin is largest in the group with the small wheals, in whom also the capillary permeability is somewhat increased and the value of the K/Ca ratio somewhat higher The average protein percentage is less in the group, the ice reaction time and the salt solution absorption time are also somewhat shorter There are nine persons with positive endothelial reactions as compared with seven in the group with larger wheals

TABLE 43—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Wheal at the Site of Injection of Thyroxin*

Reaction to Thyroxin, Wheal, Mm	Reaction to Thyroxin, Flare, Mm	Blister Time, Hours	Capillary Perme- ability	Inflammatory Index	Calcium Mg	Potassium, Mg	K/Ca Ratio	Protein, Mg	Ice Reaction Time, Seconds	Endothelial Reaction	N ₂ O Absorption Time, Minutes	Deaths
5.35	3.00	7.72	67.3	9.47	10.2	19.3	1.9	8.341	9.6	11+ 9—	75.2	6
12.5	0.92	6.95	63.9	9.38	10.3	18.1	1.75	9.338	13.8	7+ 13—	85.2	7

INTRACUTANEOUS REACTION TO THYROXIN FLARE

As twenty-nine of our patients showed no flare at the site of the injection of thyroxin, they have been grouped together, and the rest of the material has been divided into a group showing a small flare and a group showing a large flare of twenty-seven and twenty-six patients, respectively

From the curve in chart 22, it will be observed that the flare in the tuberculous group is less marked than in the "normal" and miscellaneous clinical groups previously examined, and that the deaths, as well as the cases with pleural effusion, are uniformly distributed Table 44 indicates that there is no correlation of the size of the flare with the clinical status The averages of the other determinations for the groups with the smallest and the largest flares show no striking differences and we have therefore omitted the tables

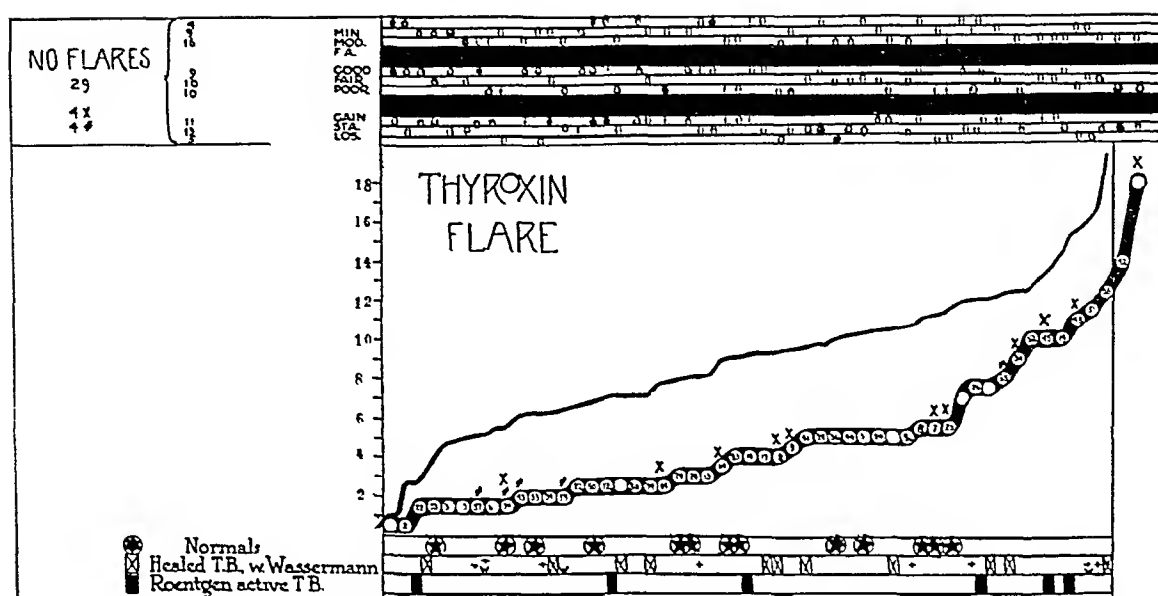


Chart 22—The curve of the intracutaneous reaction to thyroxin (flare)

TABLE 44—Comparison of the Groups with the Small, the Medium and the Large Radn of the Flare at the Site of Injection of Thyroxin, with Regard to Clinical Status

Clinical Classification of Patients	Small Flare (29 Patients)	Medium Flare (27 Patients)	Large Flare (20 Patients)
As to Type of Tuberculosis			
Minimal	13%	33%	20%
Moderately advanced	31%	37%	27%
Far advanced	56%	30%	53%
As to Prognosis	100%	100%	100%
Good	30%	60%	20%
Fair	34%	14%	42%
Poor	36%	26%	38%
As to Weight Curve	100%	100%	100%
Gaining	37%	60%	27%
Stationary	45%	30%	50%
Losing	18%	10%	23%
	100%	100%	100%

REACTION TO TUBERCULIN¹⁸ (TWENTY-FOUR HOURS)

The size of the reaction at the site of the injection of tuberculin, as measured after twenty-four hours, varied in our series from 0 to 28.5 mm. The curve in chart 23 illustrates the series. If we divide the group into those with negative or small, those with intermediate and

¹⁸ Long's Synthetic Tuberculin used

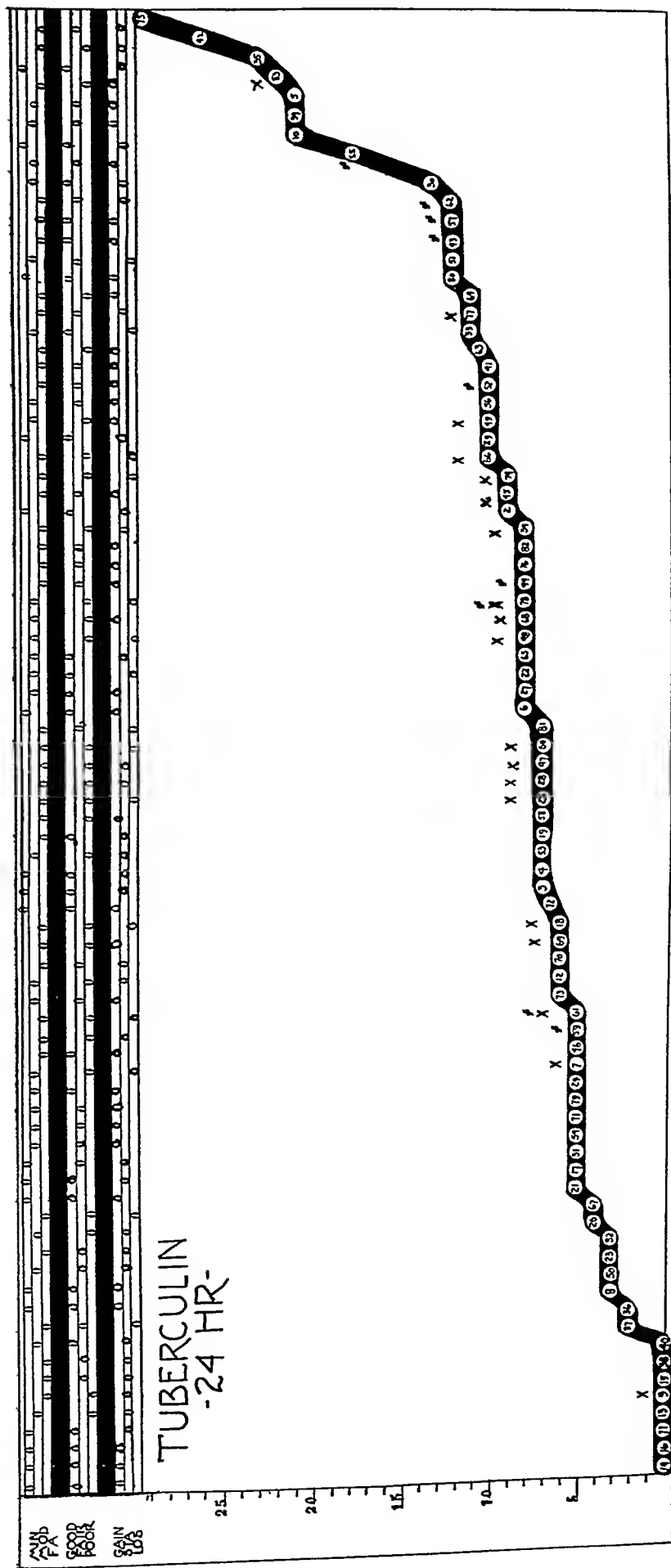


Chart 23 —The curve of the reaction to tuberculin (at twenty-four hours)

those with large reactions we find that there are more cases of minimal manifestation in the group with small reactions and more cases of far advanced tuberculosis in the group with large reactions. There appears to be absolutely no difference in the clinical prognosis as between these groups and no clearcut difference as far as the weight curve is concerned. It will also be observed that the deaths are distributed largely in the center of the curve and that the cases with pleural effusion seem to be associated with somewhat larger flares.

TABLE 45—*Comparison of the Groups with the Small, the Medium and the Large Diameters of the Reaction at the Site of Injection of Tuberculin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (24 Hours) (20 Patients)	Medium Wheal (24 Hours) (41 Patients)	Large Wheal (24 Hours) (20 Patients)
As to Type of Tuberculosis			
Minimal	45%	14%	15%
Moderately advanced	25%	36%	30%
Far advanced	40%	50%	55%
	100%	100%	100%
As to Prognosis			
Good	45%	29%	35%
Fair	35%	24%	45%
Poor	20%	47%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	41%	55%
Stationary	55%	31%	35%
Losing	10%	28%	10%
	100%	100%	100%

In table 46, in which the groups at the extreme ends of the curve are compared, it may be noted that in the low group there is more potassium and less cholesterol and a smaller wheal at the site of the injection of thyroxin, but a flare somewhat larger. The salt solution absorption time is less, but the value of the corpuscles/plasma ratio is somewhat increased.

REACTION TO TUBERCULIN (PERSISTENT)

When we now take into consideration the persistency of the reaction (chart 24), we again find that there is no direct relation to the deaths. The relation to clinical status is shown in table 47. Again, the patients with the persistent and most marked flares (upper end of the curve) show a preponderance of cases of far advanced tuberculosis, there is apparently little difference between the groups as to prognosis, and the weight curve is most favorable at the end representing the most persistent and largest reactions.

TABLE 46—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Reaction at the Site of Injection of Tuberculin*

Reaction to Tuberculin, Mm	Blister Time, Hours	Capillary Permeability	Calcium, Mg per 100 Cc	Potassium, Mg	K/Ca Ratio	Protein, Mg	Cholesterol, Mg	Reaction to Thyroxin, Wheel, Mm	Reaction to Thyroxin, Flare, Mm	NaCl Absorption Time, Minutes	Corpuscles/Plasma Ratio	CO ₂ Combining Power	Deaths
22	77	67	103	202	196	83	185	81	41	65	413	563	3
147	7	67	102	187	184	8992	207	93	29	90	387	556	3

TABLE 47—*Comparison of the Groups with the Persistent Small, Persistent Medium and Persistent Large Reaction at the Site of Injection of Tuberculin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Reaction (20 Patients)	Medium Reaction (42 Patients)	Large Reaction (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	14%	30%
Moderately advanced	40%	43%	5%
Far advanced	30%	43%	65%
	100%	100%	100%
As to Prognosis			
Good	40%	31%	45%
Fair	25%	35%	25%
Poor	35%	34%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	20%	50%	45%
Stationary	65%	31%	40%
Losing	15%	19%	10%
	100%	100%	100%

TABLE 48—*Comparison of the Groups with the Negative, the Medium and the Marked Tuberculosis Complement Fixation, with Regard to Clinical Status*

Clinical Classification of Patients	Negative Fixation (20 Patients)	Medium Fixation (37 Patients)	High Fixation (20 Patients)
As to Type of Tuberculosis			
Minimal	50%	16%	0
Moderately advanced	30%	30%	40%
Far advanced	20%	54%	60%
	100%	100%	100%
As to Prognosis			
Good	55%	40%	5%
Fair	15%	32%	45%
Poor	30%	28%	50%
	100%	100%	100%
As to Weight Curve			
Gaining	30%	48%	40%
Stationary	55%	35%	30%
Losing	15%	17%	30%
	100%	100%	100%

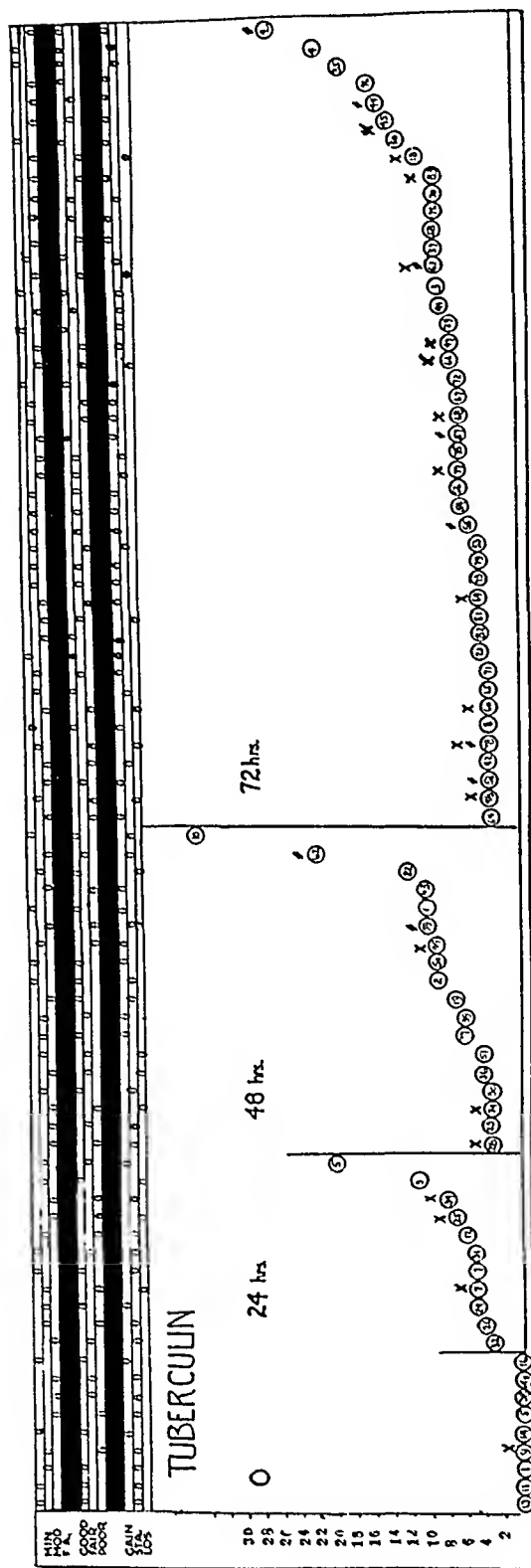


Chart 24—The curve of the reaction to tuberculin (persistent)

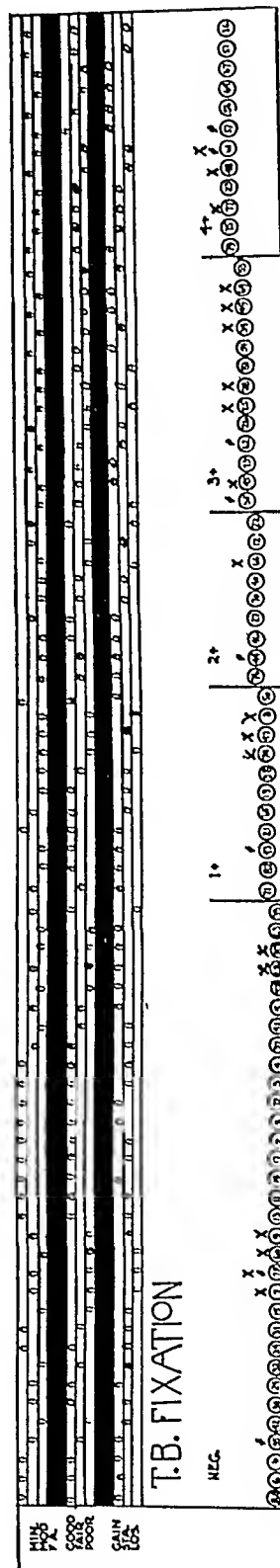


Chart 25—The curve of tuberculosis complement fixation

TUBERCULOSIS COMPLEMENT FIXATION

As the complement fixation reaction so largely follows the globulin and Daranyi reactions, we have prepared only a curve (chart 25) of the material, and have not made tables of the results of the examinations of the patients at the extreme ends of the curve. When we classify our material on the basis of this reaction, we find that the group with the negative reactions contains more cases of minimal manifestation, and the group with the most marked reactions, only cases of moderately advanced and far advanced tuberculosis. The prognosis is best in the low group and becomes increasingly poor as we proceed to the group with more marked reactions. There is no apparent relation to the weight curve.

C CLINICAL STUDY OF ALTERATIONS IN THE PERMEABILITY OF THE CAPILLARIES IN PATIENTS WITH TUBERCULOSIS

The material presented here makes it apparent, we believe, that so far as the patient with pulmonary tuberculosis is concerned, increased inflammatory reactivity is usually associated with increased clinical activity. With lessened constitutional reactivity, the clinical course is relatively benign. It is self-evident that one must keep in mind the many exceptions, the fact that the tuberculous lesion may be cured by absorption, that many of our forms of therapy make use of stimulation, etc.

Practically, our therapy consists in the effort to support normal and inherent forces of resistance either by insuring rest and proper food or by recourse to methods of moderate stimulation by physical agents.

Theoretically, three major lines of therapeutic approach to the problem of tuberculosis can be discerned. There is first and foremost the field of specific immunity, with the attack directed toward the virus, of late, the cellular aspect of the problem is receiving more attention. The second is fundamentally chemotherapeutic in the specific sense of Ehrlich. Here, again, it is the specific destruction of the virus that is the immediate goal, the reaction of the tissue being considered only to the degree that the agent shall not of itself be too toxic. Even this apparently straight line of attack is being seriously questioned, and modern investigators (the recent paper of Seifert,¹ for instance) would now place much greater emphasis on the reactions of the tissue to the injection of the so-called specific therapeutic agent. Finally, a third line of approach takes cognizance of the reaction of the tissue, with the endeavor directed toward promoting beneficial reactions and suppressing unfavorable ones. Perhaps the enzymatic destruction of bacteria, a

1 Seifert, W. *Klin. Wchnschr.* 7 1497, 1928

both epinephrine and pituitary⁹ in our experiments on lymph. The former has the disadvantage that it has so marked an effect on sympathetic nerve endings, increases the metabolic rate and, particularly in the tuberculous, may result in paradoxical effects. Dextro-epinephrine might obviate some of these defects. Pituitary seems to act well when injected in slowly absorbable form. It has the additional advantage that its effect is apparent even on irritated capillaries, when epinephrine fails. As the effect of these agents on capillary permeability is of considerable interest, we have performed an experiment in a dog, in which epinephrine (1 mg) and pituitary in oil (dosage corre-

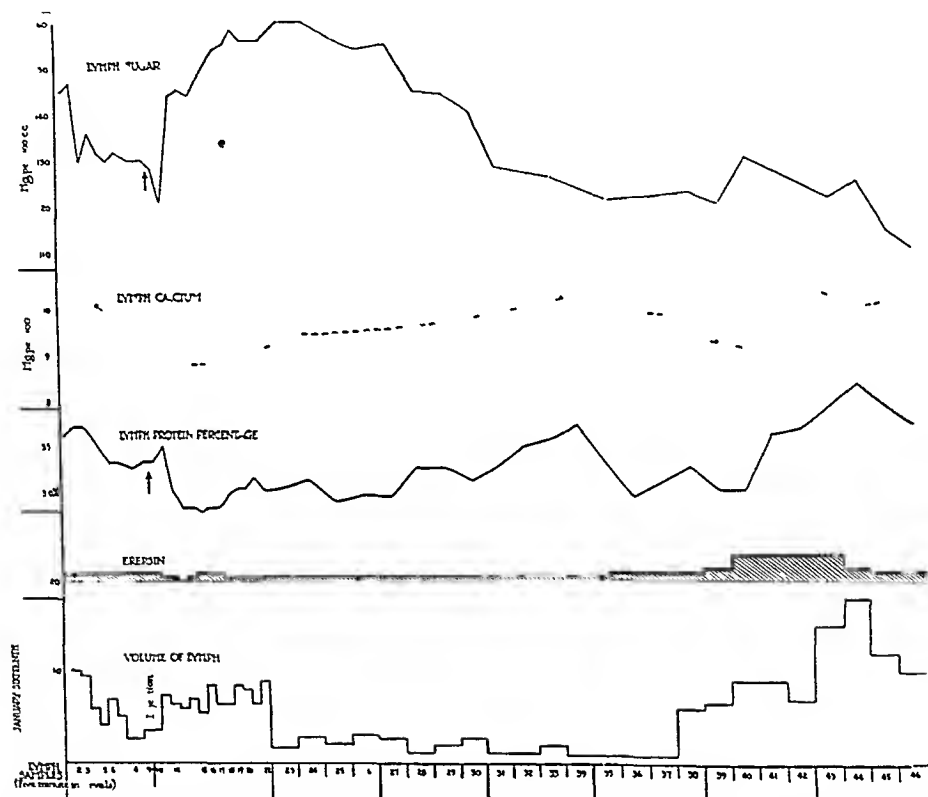


Chart 1—Effect of injection of epinephrine and pituitrin on lymph volume, lymph concentration, lymph sugar, lymph calcium and erepsin

sponding to one therapeutic dose in man) were given intramuscularly. The long continued diminution of the lymph flow after the primary increase due to increased blood pressure and the diminution in the concentration of protein indicate the change in permeability. The lowering of the calcium of the lymph is in line with this change.

Calcium—The value of the administration of calcium is problematic. The fault is not necessarily in a deficiency of calcium in the fluids, but in the fact that calcium, because of the vegetative status, is not fixed by the cells. The mere increase of the calcium of the plasma

⁹ Petersen, W. F., and Hughes, T. P. *J. Biol. Chem.* 66: 229, 1925.

produced by the administration of calcium can have little effect, nor will the use of parathyroid hormone be of avail (as recently demonstrated by Gordon, Roark and Lewis,¹⁰) because in that case one is merely taking calcium from tissue reserves to increase it in the fluids of the body. Nevertheless, it may be useful in cases in which a relatively low calcium level can be demonstrated in the plasma and the tissues are able to fix the excessive calcium offered them.

Diminution of the Activity of the Sex Glands and of the Thyroid Gland—Diminution of the activity of the sex gland in women is of obvious therapeutic importance, not only with the idea of sterilization and the avoidance of pregnancy, but on the basis that menstruating tuberculous women are more apt to have activation of the tuberculous process. The effect of thyroid activity is less apparent and still problematic. Coulaoud¹¹ described an activation of tuberculosis following the administration of thyroid extract. On general principles, lowering of the metabolic rate might be useful in cases in which one is already dealing with an increase due to the infection. The relative benignancy of tuberculosis in castrated animals and man has been established.

Therapeutically, measures designed toward the reduction of such endocrine activity are available. In the female, at least, a transient or permanent sterilization by means of the roentgen ray is easily carried out.

Finally, we must consider the production of a peripherally localized autonomic disturbance. In a series of papers, Muller and one of us (W F P)¹² demonstrated the close autonomic interrelation of the splanchnic area and the peripheral (skin and muscles) region. Stimulation of the one (parasympathetic status) is promptly followed by sympathetic orientation in the other area. Thus, if the skin is made parasympathetic by stimulation (a burn, an intracutaneous injection, etc.) the splanchnic area becomes sympathetic in its general tonus. If, for instance, one wishes to alter the vascular status of a peritoneal tuberculosis, this may be done by producing a superficial effect on the skin. As a matter of fact, this has been suggested empirically in the treatment of tuberculous peritonitis, an ultraviolet burn of an area approximately 10 by 10 cm being used.

One has, then, a series of measures available which, either singly or in combination, might influence the general reaction of the tuberculous person by altering the rate of absorption of toxic material from the foci of the disease.

10 Gordon, B., Roark, J. L., and Lewis, A. K. Effect of Parathyroid Hormone on Certain Signs and Symptoms in Tuberculosis, *J. A. M. A.* **86** 1683 (May 29) 1926.

11 Coulaoud, E. *Medecine* **3** 627, 1923.

12 Muller, E. F., and Petersen, W. F. *Klin. Wchnschr.* **5** 1025, 1926.

field of endeavor that has occupied Russian investigators chiefly, should be mentioned. A recent paper of Platonov² is one of a group that deals with a possible therapy along these lines.

We do not wish to enter into a theoretical discussion of any length in this part of the work, but we should like to emphasize the third method of therapeutic approach, namely, the endeavor to change the reaction of the host toward the infection. In this problem, the question of the capillary permeability (to proteins, etc.) immediately comes to the foreground and it is only this phase that we wish to discuss at this time. Four premises are to be taken into consideration.

1. Schade³ recently determined that the reaction of tuberculous tissue is toward the acid side (p_H of 6.5) exactly at the optimum for the growth of tubercle bacilli. The capillaries normally respond to an acid reaction by dilatation and increased permeability.

2. The autonomic nervous system, as part of the general vegetative balance is obviously involved. Not only have the studies of Guth,⁴ Glaser⁵ and others made this probable, but the pioneer work of Pottenger in this country in relation to symptomatology emphasized it. Unfortunately, conflicting concepts and terminology have obscured the work in this field. Epinephrine makes the capillary endothelium less permeable. It is, however, the representative agent for producing sympathetic effects. The "sympathetotonic" person, on the other hand, has more permeable capillaries and the blood pressure may be low. We think of the state of tissues with contracted vessels and less permeable capillaries as the typical rest stage. Yet in many persons the injection of epinephrine hydrochloride lowers the blood pressure and increases the permeability. The so-called "vagetonic" person usually has a higher blood pressure, a lower metabolic rate and less permeable capillaries. Yet stimulation of so-called parasympathetic nerves commonly results in dilatation of the vessels and increased permeability, i. e., tissue activity. Obviously, much of the confusion results from the transfer of strictly anatomic concepts and terms to the autonomic nervous apparatus, instead of starting out on a purely functional basis (see the discussion of Kraus' concept). Relatively impermeable capillaries (an effect of epinephrine and pituitary?) are usually found associated with relatively chronic tuberculosis, and greater permeability with active tuberculosis (effect of thyroid?).

3. Even specific agents (tuberculin, sodium aurothiosulphate, sodium cinnamate, etc.) act on the capillaries, usually rendering them

2. Platonov, G. J. *Infect Dis* **14** 549, 1926.

3. Schade, H. *Ztschr f d ges exper Med* **49** 334, 1926.

4. Guth, E. *Beitr z Klin d Tuberk* **60** 39, 1924.

5. Glaser, W. *Beitr z Klin d Tuberk* **55** 390, 1923.

more permeable for a time, and later diminishing their permeability. The focal reaction, whether in the form that is obvious clinically, or consisting merely of practically imperceptible biologic reactions following in the wake of minute doses of various agents, is a reaction that depends on changes in the permeability of the capillaries about the focus.⁶

4 Various biologic influences (endogenous or exogenous), among them menstruation, the effect of the season, etc., which are distinctly associated with increased permeability and autonomic instability are frequently found associated with distinct clinical evidences of activation.

The conclusion might seem warranted that increase in capillary permeability, however produced, unfavorably influences a tuberculous process.

METHODS OF DIMINISHING PERMEABILITY

Granted these simple premises, how can one proceed to bring about diminished permeability of the tissues? Several possibilities may be considered.

1 Alkalinization

2 Agents acting directly on cell membranes, chiefly epinephrine and pituitary (perhaps insulin)

3 Increasing the calcium of the plasma

4 Diminishing the activity of the thyroid or of the sex glands

5 Producing a peripheral regional (skin and muscles) autonomic stimulus with resulting compensation in the visceral area

Alkalinization—In its general effects alkalinization must make tissues less permeable, for the converse, local acidosis, makes the capillaries dilate and the endothelial cells more permeable. Modrakowski and Lentz have recently confirmed this.^{6a} It must be kept in mind that with the usual methods at one's disposal, alterations produced by therapeutic measures (administration of citrates, the Sippy diet, etc.) are never pronounced and, at best, the CO₂ combining power is increased to only a minor degree. Jordan's work⁷ indicates that there may be considerable difference in the effect, however, in different persons.

Epinephrine and Pituitary—Both epinephrine and pituitary diminish the permeability of cells, even in high dilution. Langer⁸ demonstrated this effect for epinephrine and we showed the same effect for

6 Levinson, S. A., and Petersen, W. F. *Am Rev Tuberc* **15** 6, 1927

6a Modrakowski, G., and Lentz, R. Abstracts, International Physiological Congress, Boston, 1929, p. 184

7 Jordan, S. M. Calcium Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, *J. A. M. A.* **87** 1906 (Dec. 4) 1926

8 Langer. *Ztschr. f. physiol. Chem.* **118** 1, 50 and 96, 1922

May one at the same time make the soil less favorable for the growth of the organism? This is a question that only long experience and experimentation will solve. The presumptive evidence is in favor of this view, and for the following reasons. The reaction at which the tubercle bacilli seem to grow best in the human organism is at a p_H of 6.7, i.e., slightly on the acid side of neutrality. This is the range at which Schade found the caseous material of the tubercle. If one is able to alkalinize the tissues or to create a tendency toward restoration to the alkaline side, the soil might, it seems, be made less favorable.

CLINICAL OBSERVATIONS

THE INJURIOUS EFFECT OF INCREASE IN PERMEABILITY

The first two cases concern twin sisters, 23 years of age. Both had been under observation at the municipal dispensaries for a long time and for a short time were at the Municipal Sanitarium.

Clinical History of Sister A—The illness began with pleurisy in 1920, in 1922, there was cough with loss of 20 pounds (9 Kg), night sweats, etc. In addition, the patient had numbness and twitching of the right arm, with some plasticity, and later of the entire right side, but this had gradually lessened. She had several convulsive seizures in February, 1924. The family history was negative. On examination, it was noted that the right shoulder drooped, and that there was marked degeneration of the subcutaneous tissues of the right arm, which was paralyzed. The condition of the lungs indicated a far advanced "C" (Turban III, right IV, left III). The temperature was 101 F in the afternoon, the pulse rate was 120. Tubercle bacilli were found in the sputum. The urine was normal. The Wassermann reaction was negative. The tuberculosis complement fixation was ++. The hemoglobin content was 70 per cent. The red cell count was 4,750,000, and the leukocytes numbered 11,300.

The patient entered the Research and Educational Hospital in June, 1925, with essentially the same physical conditions. The roentgenogram revealed cavitation of both upper lobes and an extensive parenchymal infiltration throughout both lungs.

The infection, as determined by further investigation, probably had occurred during childhood by transmission from a seamstress who frequently worked and lived in the family. She had had an apparently active tuberculosis, and the twin sisters frequently had been in contact with her for considerable periods.

On admission, the weight of patient A was 76 pounds (34.5 Kg). In the graphic chart of this patient (chart 2) it may be noted that the temperature and the pulse rate during the control period of observation fluctuated within a constant range. On July 4, the patient was inadvertently exposed to rather intense sunlight for several hours, and an activation was immediately apparent, the average of the maximal temperatures increasing 0.7 F.

On July 13, 15 and 17, the patient was given 2 mg of pilocarpine in oil (intramuscular injections). Despite the fact that peripheral dilatation should be followed by a decrease in temperature, there was a marked increase both of temperature and of pulse rate (chart 2). Two weeks after the first injection of pilocarpine, the patient began to complain of severe headache, the temperature

increased markedly, delirium developed thirty-three days after the injection, and one week later the patient died with all the clinical and laboratory evidences of tuberculous meningitis

It may be of interest to observe in chart 2 that intramuscular injections of epinephrine in oil were given the patient after the onset of the tuberculous meningitis and a striking effect on the basal metabolic rate was noted. So, too, the injection of large doses of dextro-epinephrine (5 mg in oil on alternate days) may have influenced the temperature for a short period before death

Autopsy (by Dr R H Jaffe) —The body was that of a fairly well-built, extremely emaciated female. The skin was pale yellow-gray with several livid patches on the back. The subcutaneous fat was reduced to a yellow-brown layer, from 3 to 5 mm thick.

The lungs were adherent to the thoracic wall by a fibrous band, especially in the upper lobes. The lower margins of the lower lobes were distended and rounded off. The posterior part of the right upper lobe contained a large irregular cavity from 2 to 3 cm in diameter, filled with a small amount of yellow-green fluid. The walls were smooth and gray-red. Elevations corresponding to the larger vessels were present. The cavity communicated with the larger bronchus of the upper lobe. There were groups of acinose yellow-gray nodules in the center of the right lower lobe. The left lung showed an irregular cavity in the posterior part of the upper side of the lower lobe. It was 0.5 cm in diameter and its walls were similar to those of the cavity described. About this cavity in the left lung were several small yellow nodules in areas of gray-red consolidation. Near the base of the left lower lobe was a small, round cavity with smooth, gray-white fibrinous walls, about 9 mm in diameter. Attached to this cavity was a small, fibrous, calcified nodule with branches of scar tissue about it. The lymph glands of the hilum about the tracheal bifurcation were slightly enlarged, gray-red and soft.

The heart weighed 175 Gm. The pericardial cavity contained 100 cc of clear, yellow fluid. The left ventricular wall was 12 mm in diameter. The right ventricular wall was 4 mm in diameter. The myocardium was red-brown and soft. The endocardium of the left ventricle showed a whitish thickening over the septum. There were no changes in the valves. The aortic circumference above the valves was 58 mm. Small yellow elevations about the coronary openings were found. Large, yellow-white plaques were found in the ramus ascendens of the left coronary artery.

The spleen weighed 88 Gm. It was soft and dark red, and the cut surface showed distinct structure.

The liver weighed 905 Gm. The surface was smooth and gray-brown, with irregular yellow patches on the convexity of the right lobe. These patches extended about 1 cm into the liver tissue. The cut surface showed almost no structure.

The suprarenal glands showed the cortex gray-white, with yellow nodules, and the medulla deep brown.

The kidneys weighed, left, 135 Gm, right, 110 Gm. The capsules stripped easily. The surface of the left kidney showed distinct fetal lobulation. The cortex was gray-red, the medulla dark red.

The stomach contained a small amount of gray fluid. The mucosa had been destroyed by postmortem changes.

The cecum contained several round, superficial ulcerations from 3 to 5 mm in diameter. The edges were notched. The mucosa was dark red, no changes appeared in the other parts of the intestine.

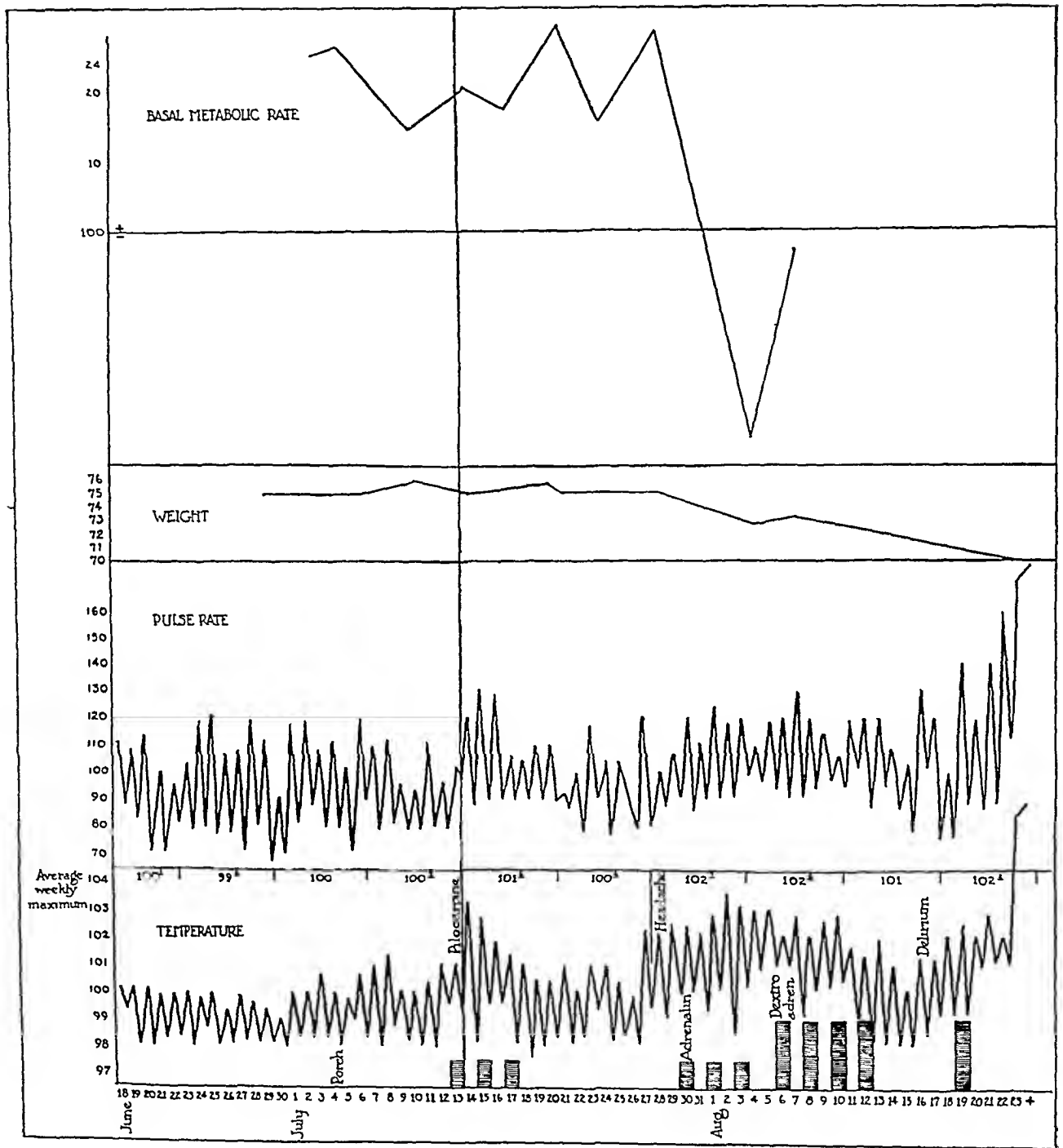


Chart 2—Clinical record of sister A, who died from tuberculous meningitis
The patient was treated with pilocarpine and epinephrine

The ovaries were small with deep depressions on the surface. They contained no corpora lutea. There was a small cyst in the right ovary.

The uterus was small. The mucosa was anemic.

The pancreas weighed 72 Gm. It was about 17 cm long. The color was gray-red.

The dura mater was smooth and gray-white. Dark red blood clots were observed in the longitudinal sinus.

The brain was swollen. The convolutions were flat, the leptomeninges over the convexities were deep red. Over the base of the brain was a large amount of yellow-green, gelatinous exudate, covering the pons and filling the space about the infundibulum. Many small, gray nodules occurred along the arteria cerebri media and diffuse nodules occurred near the pole of the temporal lobe. The ventricles were distended and filled with a cloudy, gray-red fluid. The brain tissue was soft. A small thickening was observed in the meninges near the median edge of the left convexity over the upper part of the anterior central convolution. Incisions here revealed a small yellow nodule from about 3 to 5 mm in diameter, lying between the gray and the white matter. The nodule stood out, separated from the surrounding tissue by a fine gray line.

Anatomic Diagnosis—The diagnosis included the following conditions: large tuberculous cavities in the right upper and left lower lobes, fresh acinose eruptions in the center of the right lower lobe, submiliary tubercles in the surroundings of the cavity in the left lower lobe and an encapsulated tubercular lesion in the basal part of the left lower lobe, tuberculous meningitis, acute edema and hydrocephalus internus of the brain and old solitary tubercle in the anterior central gyrus of the left convolution, fresh tuberculous ulcers of the cecum, atrophy of the heart, cloudy swelling, edema and incipient cloudy degeneration of the liver, cloudy swelling of the kidneys and atrophy of the spleen.

Histologic Observations (Dr. Jaffé)—Spleen. Many miliary tubercles were present in the pulp. They consisted of epithelioid cells and single large giant cells.

Lungs. In the surroundings of the tuberculous cavities many acinar tubercles were found in the thickened interalveolar septums. These tubercles showed much caseation. Collagenous fibers extended between the epithelial cells of the marginal zone into the caseated centers, where they were distinguished between the tuberculous debris. Much fibrous tissue surrounded and separated the tubercles.

Brain. The nodule in the cortex of the left convexity of the brain consisted of a cheesy center, surrounded by a wall of large, round, foamy cells and lymphocytes. Between these, distended capillaries were visible. Outside the cellular zone was a capsule of dense collagenous connective tissue, stained bright red in the van Gieson sections. About this capsule was a marked proliferation of glia tissue. Distended blood-filled capillaries perforated the fibrous capsule.

Kidney. The kidneys showed little change: a diffuse capillary hyperemia of the medulla and a slight swelling of the epithelium of the convoluted tubules.

Liver. There were few submiliary tubercles. They consisted of one or two giant cells, a group of lymphocytes and a thick capsule of hyaline connective tissue, which extended into the center of the nodules.

The heart revealed marked pigmentation of the myocardial fibers. The suprarenal glands showed the lipid content of the cortex much diminished, and hyperemia of the reticulum. No changes were noted in the pancreas.

THE CONVERSE

We turn now to the converse of this picture

Clinical History of Sister B—The twin sister B entered the Municipal Sanitarium with patient A (July, 1924). She gave a history of pleuritic pains, abdominal pain, loss of 20 pounds (9 Kg), and cough, which had been present for a year. In February, 1924, she had an acute exacerbation, with chills and sweats, and was in bed for ten weeks.

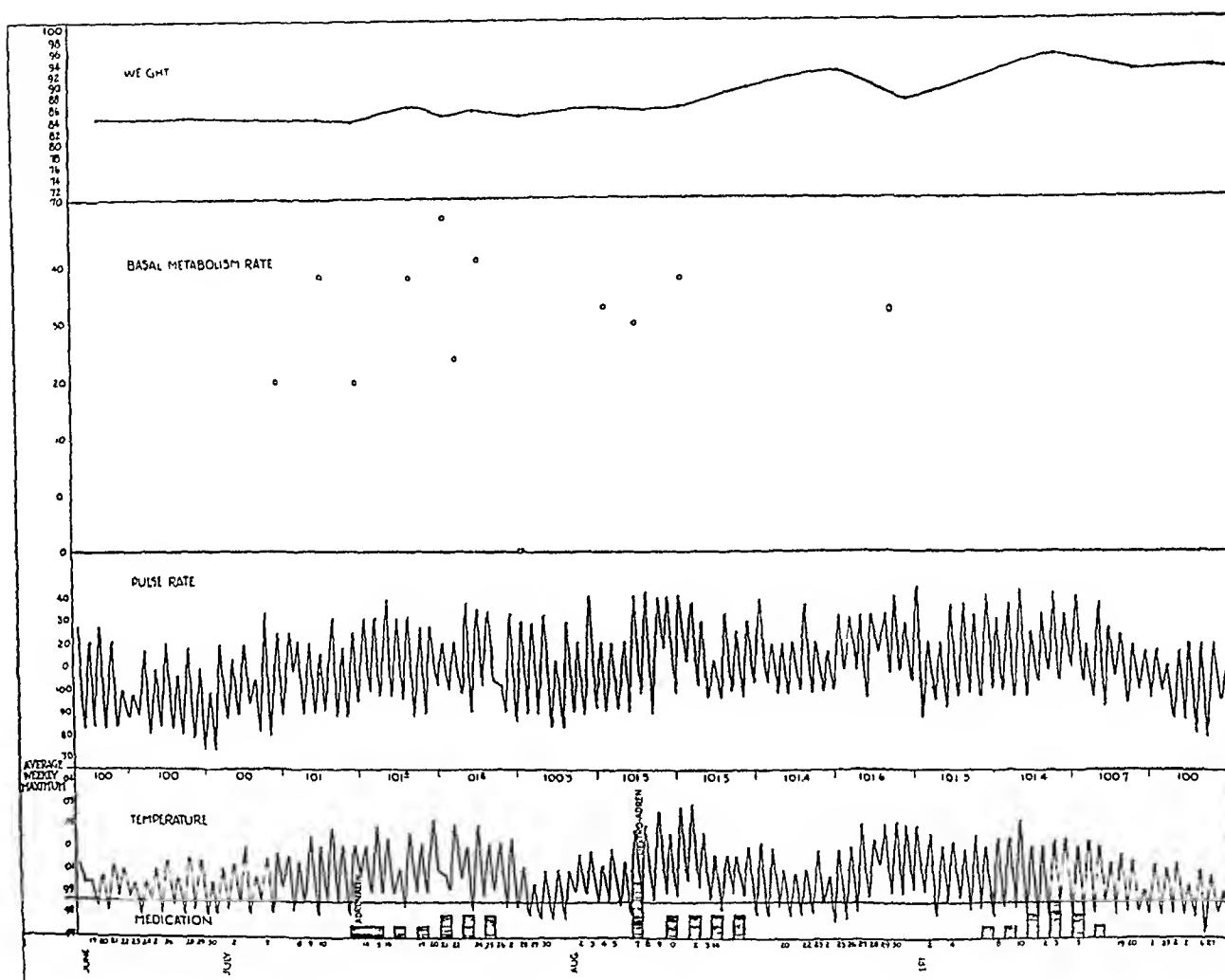


Chart 3—Clinical record of sister B, who improved on injection of epinephrine

The examination made when she entered the sanitarium revealed a pulmonary involvement classified as far advanced "B" (Turban III, left III, right II). The sputum was negative, the Wassermann reaction was negative, the tuberculosis complement fixation was +, the hemoglobin content was 75 per cent, the red blood corpuscles numbered 4,050,000 and the leukocytes 11,000 per cubic millimeter. The morning temperature was recorded as 96.4 F and the pulse rate 100.

The patient was admitted to the Research and Educational Hospital on June 18, 1924, with her twin sister and was observed under identical conditions. The physical examination at admission revealed cavitation in both upper lobes and

soft parenchymal infiltrations throughout both lungs. The weight was 86 pounds (39 Kg), i e, 11 pounds (5 Kg) more than her twin sister's, and her general condition was correspondingly better, owing to her ability to feed herself, the sister A having paralysis of the arm. The temperature and pulse curves were practically identical.

After having been under observation for two weeks, this patient also was inadvertently exposed to sunlight for several hours on July 4 and reacted with an increased temperature, as had the sister. On July 13, 14 and 15, 1 mg of

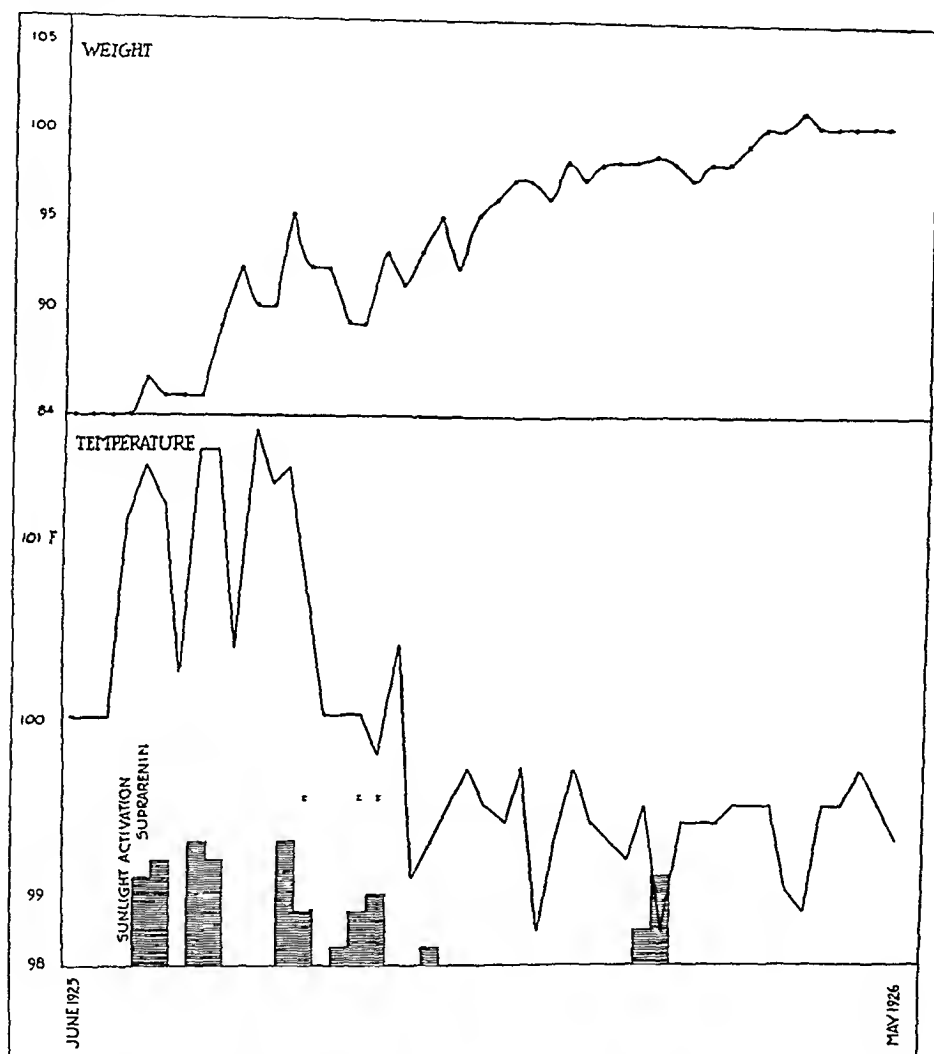


Chart 4—Condensed chart of year's observation of sister B, showing effect of treatment with epinephrine in tuberculosis activated by an overdose of sunlight

epinephrine bitartrate (in oil) was given intramuscularly, and similar injections were made on June 17 and 19. On June 21, 23 and 25, 2 mg were injected and, in addition, calcium lactate was given by mouth. After this course of injections, the temperature receded for five days. The further course of the patient's illness was relatively uneventful. Repeated injections of epinephrine were made, the patient gradually increased in weight and the temperature diminished, but the pulse rate and the basal metabolic rate remained high. The patient was discharged from the hospital in May, 1926, and was still under observation at the time

of writing. She had retained her weight (105 pounds) and the tuberculous process seemed relatively stationary (charts 3 and 4)

Conclusions—We believe that we may properly conclude that the increase in permeability induced by the pilocarpine injected (moderate dosage in oil) adversely affected the tuberculous process. It brought about increased absorption from the tuberculous foci (indicated by the increases in temperature shortly after the injections, despite the fact that the loss of temperature from the skin must have been accelerated) and with it mobilization of organisms and extension of the disease (terminal meningitis). The objection can be made that the patient was susceptible to cerebral involvement, as she had previously recovered from a solitary cortical tubercle, and that consequently the terminal meningitis represents merely a coincidence.

If increased permeability of tissue is harmful, then diminished permeability of tissue must be beneficial. This seems to be indicated in the clinical course of the twin who received injections of epinephrine. The effects on the temperature of this patient indicate a distinct improvement after each series of injections. The patient gained weight and felt stronger. We may at least conclude that in this patient the injection of epinephrine was not harmful.

It is not our intention in this paper to present clinical material from a therapeutic point of view, we wish merely to establish the experimental possibility that alterations in permeability may influence the clinical picture and that the increase in permeability that we have established as associated with increasing clinical activity may be causative of the clinical status rather than incident to it. The following case histories may be of interest in this connection.

REPORTS OF OTHER CASES

CASE 1—A young white boy, aged 9, had been ill with Pott's disease for two years. He entered the hospital the first week in January, 1926, with a psoas abscess, which was discharging profusely. For the following three months, he remained under the observation of the orthopedic staff. During this time there was a continued loss of weight with marked anemia and a progressive increase in the temperature to a weekly maximal average of 104 F (first part of chart 4).

Treatment was commenced on the first of April with a skin burn (Alpine lamp, abdominal exposure, twenty minutes, area 10 by 10 cm, distance 20 cm). A second and a third exposure were made as indicated in chart 5.

In addition, epinephrine in oil was injected intramuscularly on alternating days, beginning April 9 (five injections). The injections were not continued, because the child was emaciated and the injections caused some pain. Later epinephrine was given by mouth (dosage, 5 drops three times a day).

Sodium citrate was given continuously by mouth from April 11 until the end of May (dosage, 1 Gm three times a day).

Examination of chart 5 indicates that an improvement commenced about one week after the third period of irradiation of the skin. At about the same time, the discharge lessened and finally ceased two weeks before the patient left the hospital. It was not possible to keep the child for a long time for observation.

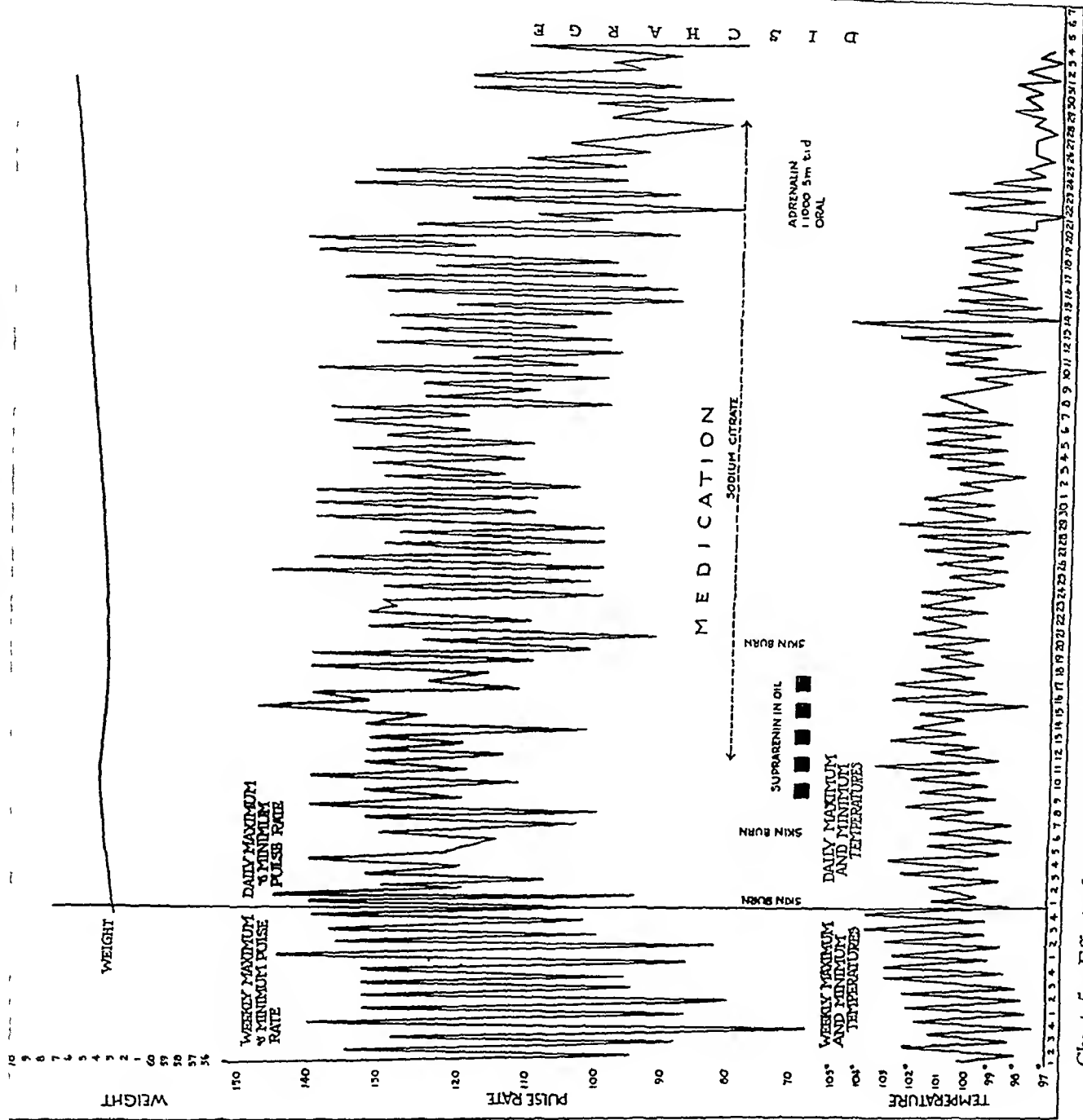


Chart 5—Effect of treatment with skin burn (Alpine lamp), epinephrine and sodium citrate (case 1)

In this patient, rest in bed and relative immobilization resulted in no improvement during a period of observation of three months. Measures instituted with the view of diminishing capillary permeability were followed by an apparent cessation of the symptoms of activity as far as the psoas abscess and the temperature of the patient were concerned.

CASE 2—The patient had been ill for at least seven years, beginning with influenza in Germany, where she had collapse therapy of the right lung with subsequent refilling at frequent intervals. She came to America in 1924. She worked hard as a maid and had suffered a breakdown in December, 1924. She was admitted to the Cook County Hospital in December, 1924, and she remained there until Aug 5, 1925, then she was transferred to the Research Hospital. The maximal and minimal weekly averages of temperature for her stay at the Cook County Hospital are given in chart 6, as well as the daily maximal and minimal temperatures for her stay at the Research Hospital.

Physical examination indicated a far advanced pulmonary tuberculosis with pyopneumothorax of the right side.

The pulse range after admission was somewhat higher than it had been at the Cook County Hospital. No change was made in the patient's routine of life. Ten days after her admission a daily dose of calcium lactate (3 Gm) was given for three days. There was an immediate effect on the pulse rate, the patient coughed more and had a poor appetite, and four days later the temperature rose to 102.4 F. The sputum was not increased. The pulse rate diminished in the following ten days, but the temperature showed a tendency to increase (marked 1 in the chart).

Epinephrine in oil, in dosage of 1 mg, was now given for five successive days, together with calcium lactate. The patient responded with a marked increase in pulse rate, a rise of temperature and an increase of sputum, was nauseated, coughed more and was sleepless and tired (marked 2 in the chart).

Obviously, the patient responded at least in part vagotonically to the agents that are ordinarily considered sympatheticotonic. This is by no means uncommon. We have observed it frequently in animals receiving injections of small doses of epinephrine in oil, and it is, of course, not uncommon in patients in whom the autonomic tonus is so altered that parasympathetic overbalance exists (Guth). The patient returned to the preinjection condition about two weeks after the injections.

On September 29, 5 mg of epinephrine in oil was given by mouth. An effect was apparent both on the pulse rate and on the temperature (the temperature had increased, however, before the ingestion. (This stage is marked 3 in chart 6).)

A definite cycle of activity took place following October 14. On October 17, the patient received a 5 per cent erythema dose of deep roentgen therapy over the noncollapsed lung. Further doses were given from October 26 to October 27, with evidences of activation following. The patient died December 13.

Anatomic Diagnosis—Right empyema pleurae and tuberculous cavities in the upper part of the right upper lobe, collapse of the right lung, smaller cavities in the left upper and lower lobes, acinose-nodose tuberculosis of the left lung, and tuberculous bronchopneumonia in the left lower lobe.

Gross Observations at Autopsy—The thyroid gland weighed 25 Gm. The upper respiratory tract showed large tonsils with deep grooves.

The right pleural cavity was filled with thick pus, and there was complete collapse of the right lung. A cavity, 5 cm in diameter, was found in the apex of the right lung, communicating with the larger bronchus. There were small areas of bronchopneumonic infiltration in other parts of the right lung. Adhe-

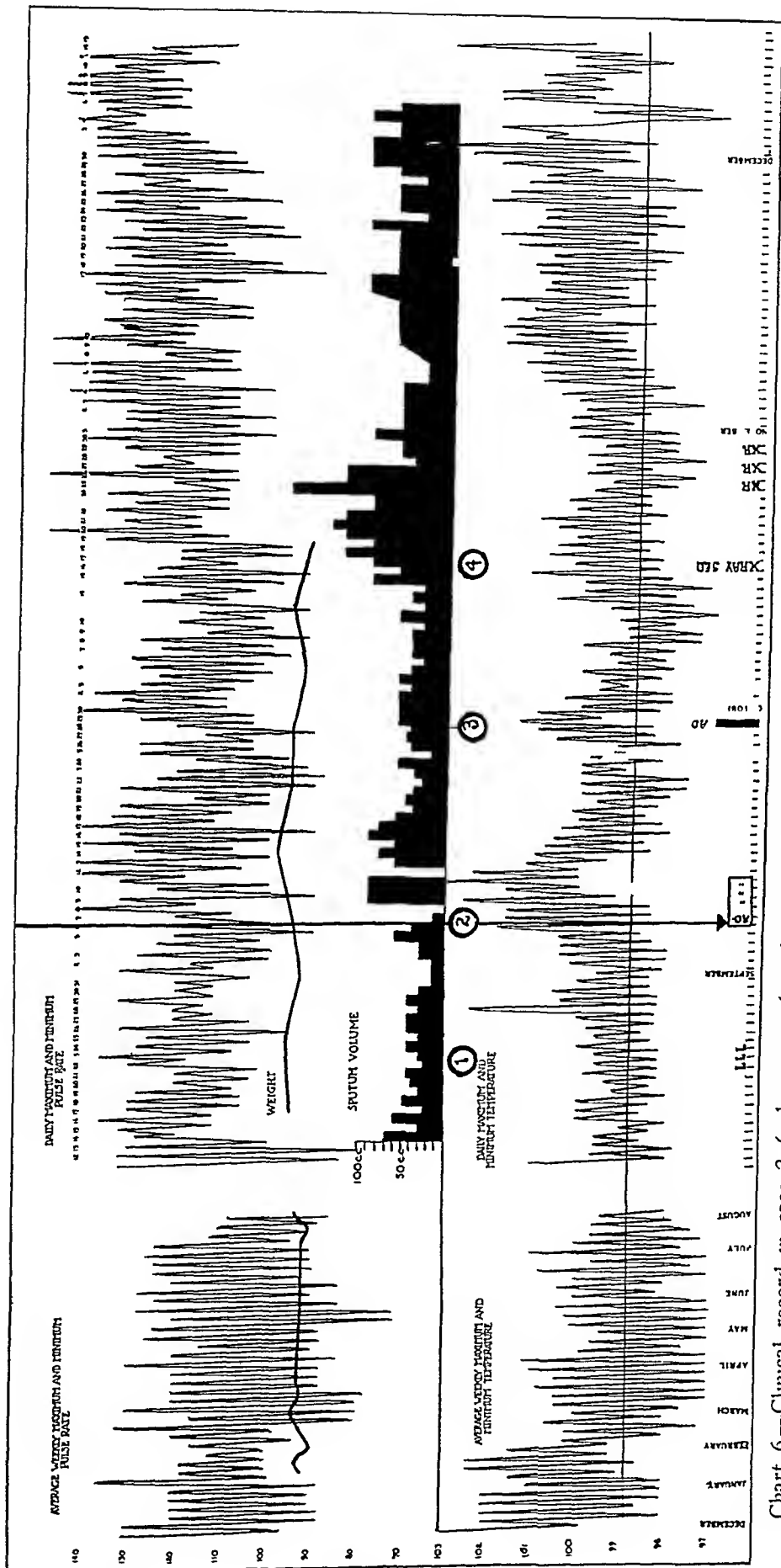


Chart 6—Clinical record in case 2 (pulmonary tuberculosis with pyopneumothorax of the right side) The patient was treated with calcium lactate, epinephrine and roentgen ray

sions were observed about the upper lobe. A cavity, 2.5 cm in diameter, was found in the upper lobe and another 1.5 cm in diameter in the upper anterior third of the lower lobe. Acinose tuberculosis appeared in the upper lobe, bronchopneumonic areas in the lower lobe.

The heart weighed 277 Gm. The left ventricle was 12 mm in diameter, the right ventricle, 6 mm. Small fatty plaques were noted above the aortic valve.

The stomach showed *état mammelonné*. The intestines showed catarrhal inflammation of the cecum with enlarged follicles, but no tuberculosis. The liver weighed 1,117 Gm. The pancreas weighed 57 Gm and was 15 cm long. The spleen weighed 3 Gm and measured 12 by 3 by 6 cm. The suprarenal glands together weighed 13 Gm. There was little lipid in the cortex, being restricted to a few yellow stripes. The right kidney weighed 140 Gm and the left 147 Gm. The uterus measured 68 by 40 by 12 mm.

Histologic Observations.—**Liver**. In the central parts of the acini there was a marked dilatation of the portal capillaries with far advanced atrophy of the liver cells, which often appeared as narrow bands with granules of dark brown pigment and pyknotic nuclei. The liver cells in the periphery of the acini were large and clear, with vesicular nuclei and fine lipid droplets. They were free from pigment. Small groups of cells contained larger fat droplets. Lipoid granules were present in the Kupffer cells. In some capillaries, an accumulation of white blood cells was found.

Spleen. The sinus was of medium width filled with blood. The malpighian bodies were small and without germinal centers, their reticulum cells were often enlarged. Few cells in the pulp contained fat granules. Fine dustlike fat was present in the capsule.

Kidney. Fine fat granules were observed in the basal parts of the epithelial cells of the proximal convoluted tubule. The cells were enlarged, bulging into the lumen. The nuclei were small and vesicular. More fat was found in the distal convoluted tubule. There was capillary hyperemia.

Heart. This organ showed capillary hyperemia, an increased amount of brown pigment about the nuclei of the muscle fibers, distinct striation of the fibers as a rule, and in a few places a granular disintegration of the fibrils.

Suprarenal Glands. There was hyperemia of the zona reticularis. The lipid content of the cortex was distinctly reduced. Larger areas were almost free from fat.

Lung. **Upper Lobe**. Epithelioid cell tubercles of different size were noted, the larger ones with central caseation. Many giant cells were present. Much fibrosis was seen about the tubercles. The tissue consisted of a homogeneous, poorly stained basement substance that often appeared as blistering bands with a few flat and elongated cells filled with fat granules. Single giant cells and small groups of epithelioid cells were embedded with this scar tissue. The epithelioid cells were distinctly free from fat. So were the giant cells. Fat became visible where central caseation was present, forming a belt of droplets about the necrotic center. In the alveoli around the tuberculous infiltrations, many round cells full of fat were seen.

In using epinephrine, one obviously encounters the fact that it acts on the autonomic nervous apparatus both as a sympathetotonic and as a vagotonic agent, and particularly in the tuberculous person the probability is rather in favor of the latter. With pituitary, one may anticipate a more certain outcome. We tried this first in combination with epinephrine as well as with a skin burn.

CASE 3—A young colored man was admitted with a clinical diagnosis of tuberculous peritonitis. The illness had begun six weeks before admission. Swelling of the abdomen had existed for approximately five weeks. The physical examination indicated a pleurisy of the left side with considerable distention of the abdomen with fluid.

After seventeen days' observation, treatment was commenced with the intramuscular injection of pituitary and epinephrine in oil. On January 20, epinephrine was given by mouth, in addition, and later more epinephrine in oil on alternating days. In addition, the patient was burned (ultraviolet dosage similar to that

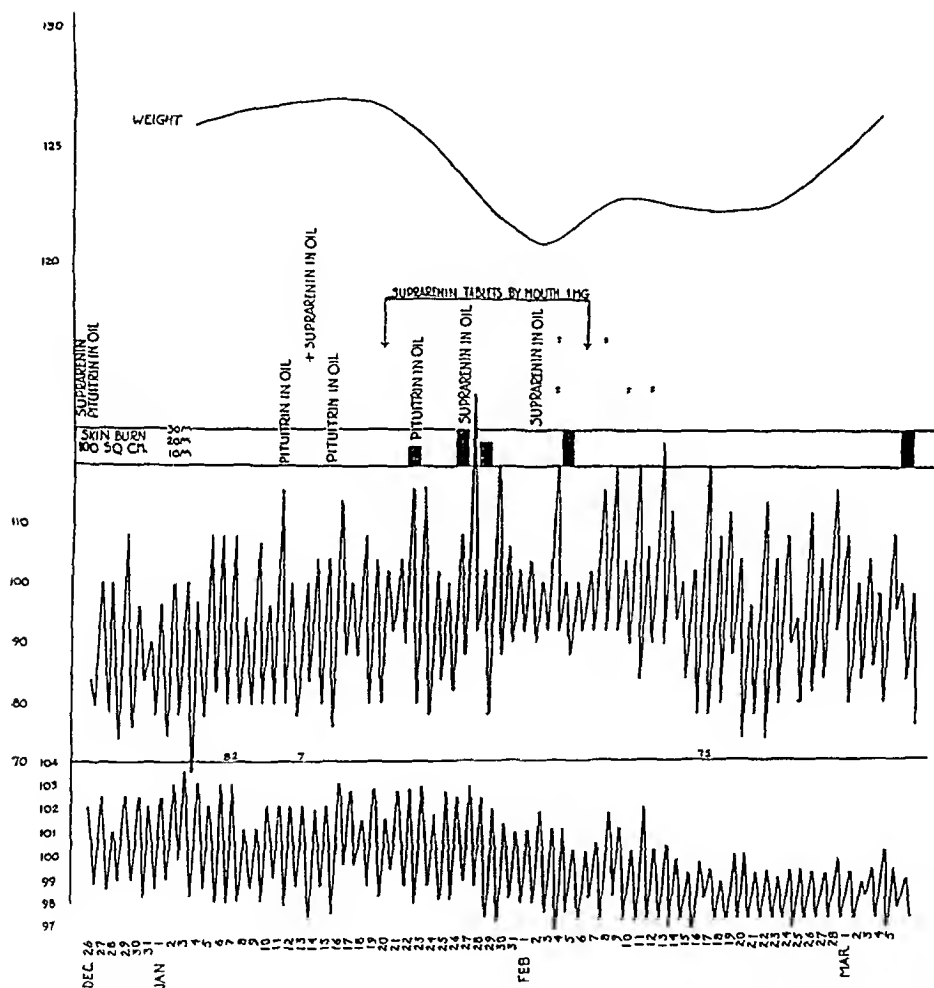


Chart 7—Clinical record of case 3 (tuberculous peritonitis and pleurisy). Transient clinical improvement is shown.

administered to patient 1) on January 22, 26 and 28, February 4 and March 5. Being heavily pigmented, the patient was resistant to ultraviolet light. The effect of the injections of the drugs on the permeability of the skin capillaries was apparent in a reduction from 0.82 to 0.72.

Following the skin burns, the fluid was promptly absorbed from the peritoneum and the patient's weight diminished 7 pounds (3.2 Kg). This was followed by a subsequent recovery, without reaccumulation in the peritoneum, and with no apparent further peritoneal discomfort (chart 7).

In this case the patient was by no means cured. Through a misunderstanding, the patient was discharged. He was readmitted April 1, this time with great distention of the abdomen. Because of the discomfort, the abdomen was opened and about 9 pounds (4.1 Kg) of fluid removed. The peritoneum was found studded with large tubercles. The patient was treated with pituitary and epinephrine in oil and later with epinephrine by mouth. This time there was no apparent effect, the patient was removed from the hospital by relatives, and we have no information concerning the outcome.

CASE 4—The patient was admitted to the Research and Educational Hospital, May 20, 1926. He was a colored man, aged 24, with a history of typical tuberculous peritonitis of five months' duration. His weight on admission was 130 pounds (59 Kg).

Physical examination and roentgen examination revealed a far advanced tuberculosis with involvement of the entire right lung, pleurisy of both the right and the left side and tuberculous peritonitis. The blood pressure was 122 systolic and 88 diastolic. On June 22, a thoracentesis was made and 60 cc of straw-colored fluid was removed. On June 25, approximately 1,500 cc of fluid was withdrawn. On December 28, another aspiration of the right chest was made and 500 cc of fluid withdrawn. On December 31 another 500 cc was withdrawn.

After a short period of observation, the patient was treated with calcium lactate, atropine and small doses of pituitary, the latter preparation practically inert, however. After the preliminary loss of weight associated with the reduction of fluid in the pleural and abdominal cavities, the weight curve was practically stationary. On November 16, three doses of an active pituitary preparation in oil were given daily intramuscularly (indicated by the heavy arrow in chart 8). The pulse rate increased, the temperature declined and the weight fell sharply. A short course of digitalis was given and later the patient was put on a Sippy diet for two weeks. The patient ultimately died, in February. The autopsy was performed by Dr J. P. Simonds, to whom we are indebted for the report.

Autopsy—Externally, the body, that of a male, appeared poorly nourished. A lymph gland low down in the neck was palpable. The axillary lymph glands were enlarged. The inguinal lymph glands were somewhat enlarged. On the medial side of Poupart's ligament was an old scar, 5 by 11 mm. The level of the abdomen was about the same as that of the chest.

The fat in the anterior abdominal wall was 5 mm thick. The intestines were everywhere matted together by dense fibrous adhesions. There were yellowish-white nodules, from 1 mm to almost 1 cm in diameter. On section, they were cheesy.

Chest, Right Side The air escaped when the chest was open. In the anterior mediastinum, in both the upper and the lower parts, were large lymph glands, cheesy on the cut surface. The largest above the diaphragm was 2 cm in diameter and 0.5 cm thick. *Left Side* The pleural cavity was obliterated by adhesions similar in density to those in the peritoneal cavity. In the lower posterior portion was a cavity between the lung and the chest wall, and the diaphragm was filled with turbid yellowish fluid, in which were many flakes of fibrin. The parietal and visceral pleurae here were covered with a thick layer of yellowish-white exudate. Elsewhere in the pleura there were easily torn fibrous adhesions. Cheesy nodules were found, the largest 7 mm in diameter. On the right side, the parietal pleura was much thickened and the inner surface was covered with a yellowish exudate. Between the parietal pleura and the right lung was a cavity filled partly with turbid fluid in which were flakes of fibrin. This cavity was partly filled with air. The parietal and visceral pleurae were adherent over the upper lobe. The lower lobes were collapsed and a yellowish exudate covered them.

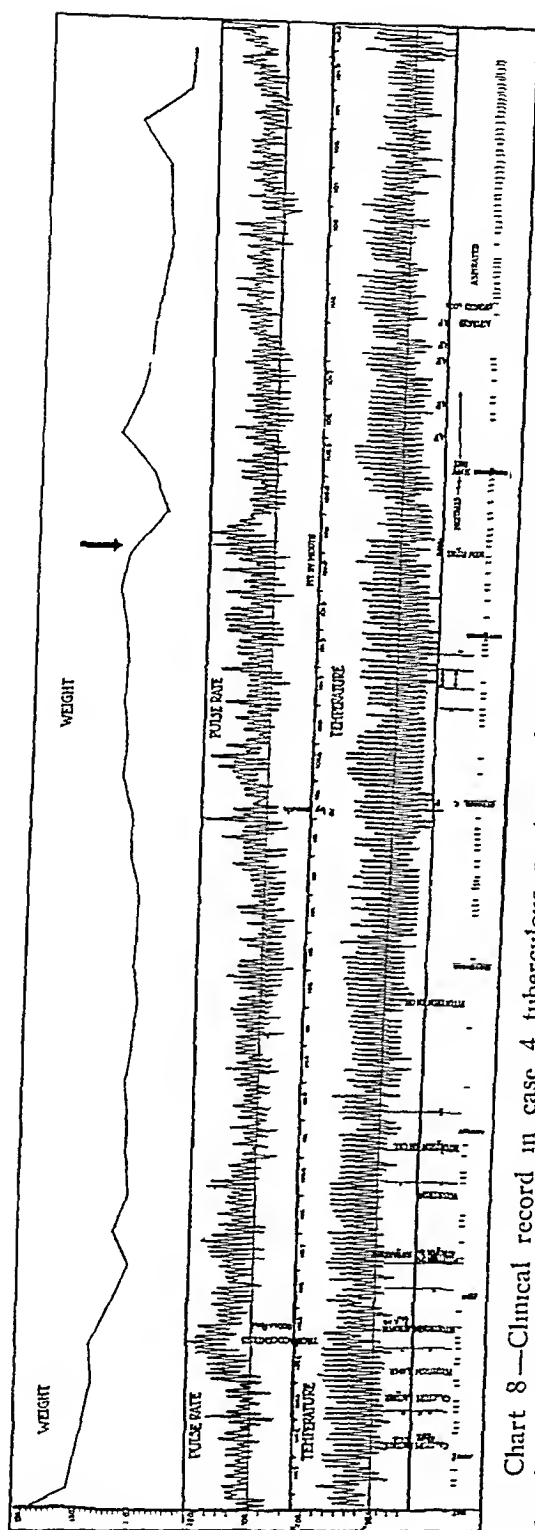


Chart 8—Clinical record in case 4 tuberculous peritonitis, bilateral pleurisy and far advanced tuberculosis of right lung) The patient was treated with calcium lactate, atropine and small doses of pituitary

The pericardium contained blood-tinged, clear fluid (50 cc) and was shining smooth and glistening

The heart was the size of the owner's right fist. The foramen ovale was closed. The tricuspid orifice admitted five gloved fingertips, the mitral, three. The heart valves were smooth and thin. The myocardium was pale grayish-red and friable, the aorta was smooth throughout.

The left lung, unopened, weighed 630 Gm. It floated in water with the lower lobe downward. The upper lobe crepitated feebly throughout. The lower lobe, upper quarter, crepitated. The remainder was noncrepitant and had the consistency and feel of spleen. The pleural surface was covered with a thick, yellow-white, fibrinous exudate. The cut surface of the upper lobe was grayish red. Frothy fluid escaped on pressure. The cut surface of the lower lobe was also grayish red. Some frothy fluid was squeezed from the upper part. Pieces cut from that portion and from the deeper parts of the remainder of the lobe floated in water.

The right lung crepitated feebly in the lower and upper part of the upper lobe. The remainder of the lung was completely collapsed and airless. The upper part of the upper lobe was adherent to the chest wall. The interlobar fissure was obliterated. The cut surface was grayish and moderately moist (upper lobe). At the hilum were numerous anthracotic lymph glands with large caseous areas. Pieces cut from the upper part of the upper lobe floated. Pieces cut from the lower lobe sank.

The spleen was markedly enlarged and firmly adherent to the diaphragm and also adherent to all other adjacent organs. It weighed from 6 to 90 Gm. There was an accessory spleen about 2 cm in diameter, in which were several millimeter-sized, cheesy nodules. The cut surface was studded with innumerable yellowish-white, cheesy masses, from 1 mm to 1 cm in diameter. There were sharply circumscribed. The cut surface was dry and cheesy. Some of the masses were round, others were lobulated and irregularly confluent.

The liver was large, the capsule everywhere thickened. In places, it was adherent to adjacent organs. It was firmly adherent to the diaphragm. A large part of the capsule was roughly stripped off with removal of the right lung. On the cut surface, some cheesy masses, from 1 to 15 mm in diameter, were found. Scattered throughout were numerous cavities. The largest was about 2 cm in diameter. They contained a thick, yellowish-green fluid, and their walls were from 1 to 2 mm thick. These were yellowish gray. The liver substance was soft and friable. The lobular markings were indistinct. The process had followed the bile duct.

The pancreas showed postmortem changes. The adjacent lymph glands were markedly caseous. The pancreas itself was not involved.

The right suprarenal gland was markedly enlarged. It was almost transformed into a yellowish, cheesy mass. No suprarenal tissue could be made out with certainty. There might have been a small narrow zone of suprarenal tissue of the extremities. The left suprarenal gland was also replaced by a yellowish, cheesy mass.

The stomach was free from ulcerations. The peritoneal surface was studded with cheesy masses.

The right kidney was larger than normal. The capsule stripped easily leaving a smooth surface. There was fetal lobulation. The cortex showed numerous red areas the size of a pin point. The cortex measured from 5 to 7 mm in thickness. The markings were indistinct. Two separate and distinct pelvises were revealed each opening into its own ureter, the ureters united before entering

the bladder In one papilla was a millimeter-sized cheesy mass A larger cheesy mass 6 by 8 mm was seen in another, and in three papillae the cheesy masses, 2 by 5 mm, were observed The left kidney was somewhat larger than normal The capsule stripped easily The surface was the same as in the right kidney The cortex was from 5 to 8 mm thick The cortical margins were not normally distinct The bladder showed nothing abnormal

Anatomic Diagnosis—Generalized tuberculous peritonitis, tuberculosis of the abdominal, retroperitoneal and mediastinal lymph glands, disseminated tuberculosis of the spleen, tuberculosis of the accessory spleen, tuberculous cholangitis, pyopneumothorax, chronic tuberculous pleurisy, bilateral, compression atelectasis of the lower lobes of both lungs, tuberculosis of the right kidney, double pelvis and urethra of the right kidney, disseminating tuberculosis of the liver, cloudy swelling of the liver and the kidneys, fetal lobulations of the kidney, and tuberculosis of both suprarenal glands

Histologic Observations—Right Lung The pleura was covered with a thick layer that in the outer portion was fibrinous and in the deeper parts caseous The endothelium covering the pleura was completely lost There was an attempt at organization of the necrotic material resting on the pleura The pleura itself was thickened, edematous and diffusely infiltrated with lymphocytes, large mononuclears and occasional plasma cells The blood vessels were widely dilated and had thin walls The lung tissue in this section showed the alveoli collapsed There was much pigmentation with coal dust The bronchi showed considerable desquamation of the epithelium and many contained a finely granular or fibrillar material, in which were scattered polymorphonuclear leukocytes In the collapsed lung tissue were a number of miliary tubercles

Liver Near the center of the section of the liver was a cavity in which was coagulated granular material, some of which was yellow The inner part of the wall of this cavity was necrotic and caseous Surrounding this was a narrow zone of fibrosis in which was an occasional tubercle Elsewhere the liver showed marked postmortem changes Many of the liver cells still showed considerable fat Scattered irregularly through the section was a moderate number of miliary tubercles

Kidney The section of the kidney showed a large caseous area separated from the remaining kidney substance by a narrow zone of fibroblasts and lymphocytes with an occasional giant cell Elsewhere there was marked postmortem change in the tubular epithelium and a fairly uniform, moderate increase of connective tissue between the tubules Many of the tubules in the cortex contained casts The glomeruli, in general, were richer in cells than normal In some, the individual capillary loops had lost their identity and the glomerulus appeared as a rather dense cellular mass None of them showed amyloid A few glomeruli had been completely transformed in the dense hyaline tissue

Suprarenal Gland In this section there was only a small amount of recognizable suprarenal tissue The remainder was composed of a large caseous mass surrounded by a zone of fibroblasts and lymphocytes with here and there a typical tubercle

The clinical course is interesting only in that it demonstrates that these large doses of pituitrin were able definitely to depress the temperature curve for approximately one week The administration was followed by an immediate increase in the pulse rate and consequently we dealt with an added strain on a cardiac musculature already depressed

The clinical application might therefore seem dubious, but the result seems to offer proof of the theory that the diminished permeability is followed by improvement so far as the temperature is concerned. The loss of weight in this case was undoubtedly due to the transient loss of water.

That pituitary given over a long period need not be harmful in suitable cases seems probable from case 5.

CASE 5—A colored man, with far advanced pulmonary tuberculosis (large cavity in the left upper lobe), had been transferred from the Cook County Hospital. He had been under observation there from April 10, 1926, to November, 1926. During this time, his weight had declined from 123 to 110 pounds. After being under observation two weeks at the Research and Educational Hospital, he was given three successive doses of pituitary (5 units per dose, in oil, intramuscularly). The temperature diminished, but the pulse increased considerably and there was a loss of weight similar to that observed in patient 4. Later, pituitary was given once a week for five months. During this time, the weight gradually increased and the sputum diminished. For a period of three weeks, large capsules of hydrous wool fat were given. A year after admission, the weight was 140 pounds (63.5 Kg), and the clinical condition was stationary (chart 9). In view of the fact that the patient had a large left apical cavity, the desirability of collapse was considered and the patient was transferred to the surgical service. He survived the immediate effects of the operation, but died suddenly two days later.

Autopsy—The body was that of a colored man, aged 35, it was 62 inches in length and weighed 144 pounds (65.3 Kg).

The left lung had adhesions about the upper portion, and smaller adhesions about the other portions. A large irregular cavity, 9.5 by 7.5 cm. was found in the left upper lobe. The cavity was filled with thin, reddish pus. The wall of the cavity was from 0.5 to 1 mm. thick. It was grayish white, covered on the inside with flat, yellowish-white plaques. In the middle of the posterior wall was a nodule, 3 mm. in diameter, which contained a cavity communicating with the branch of the pulmonary artery. In the right upper lobe were strands of anthracotic scar tissue surrounding firm, cheesy and calcified nodules, 4 mm. in diameter. Single small nodules and areas of granular consolidation were present in the left lobe.

The heart weighed 320 Gm. The left ventricle had a diameter of 13 mm. the right ventricle one of 7 mm. The aorta measured 60 by 42 by 36 mm. Small plaques were observed in the left coronary artery, and larger ones in the arterialia abdominals.

The intestines showed irregular ulcerations extending down to the muscularis and with slightly thickened undermined edges in the cecum and lower parts of the colon ascendens. There were adhesions about the appendix, which was dilated and contained near its origin a whitish nodule, 5 mm. in diameter.

The liver weighed 1,440 Gm., and showed distinct markings. The pancreas weighed 100 Gm., the spleen, 120 Gm. The left suprarenal gland presented a light yellow cortex. The right kidney weighed 160 Gm., the left, 150 Gm. The capsule was adherent. The surface was studded with small irregular, grayish-brown nodules. A gray nodule the size of a pinhead was present in the medulla of the left kidney. The brain weighed 1,370 Gm. Besides these changes a recent thoracoplastic operative wound was observed, with resections of half of the first left rib.

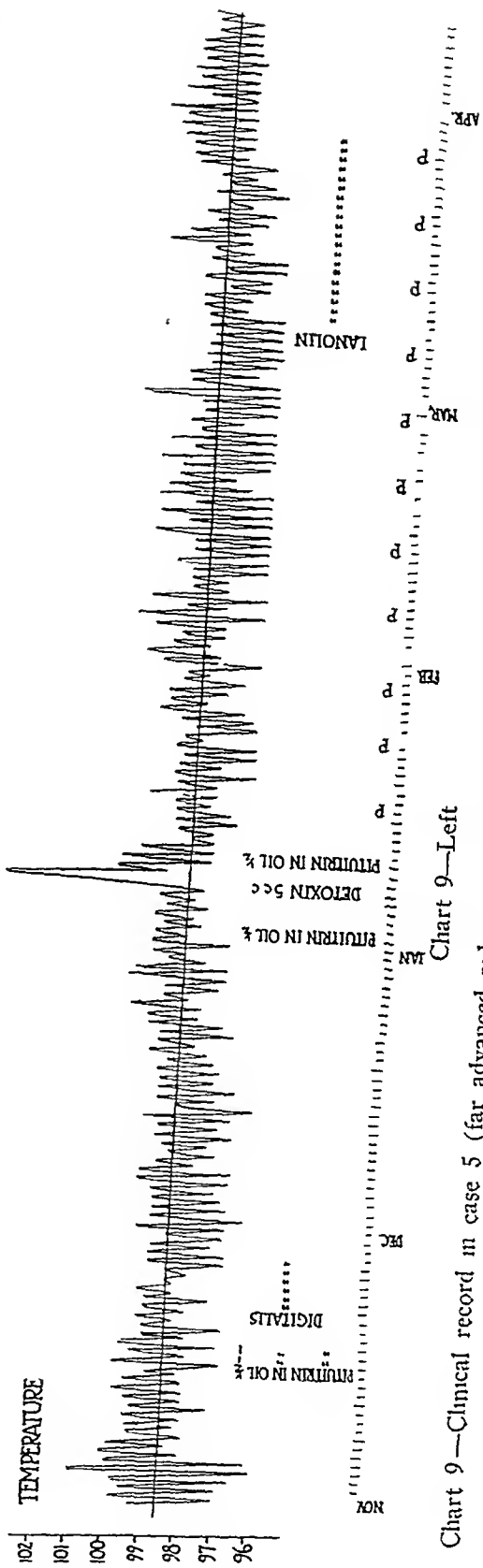
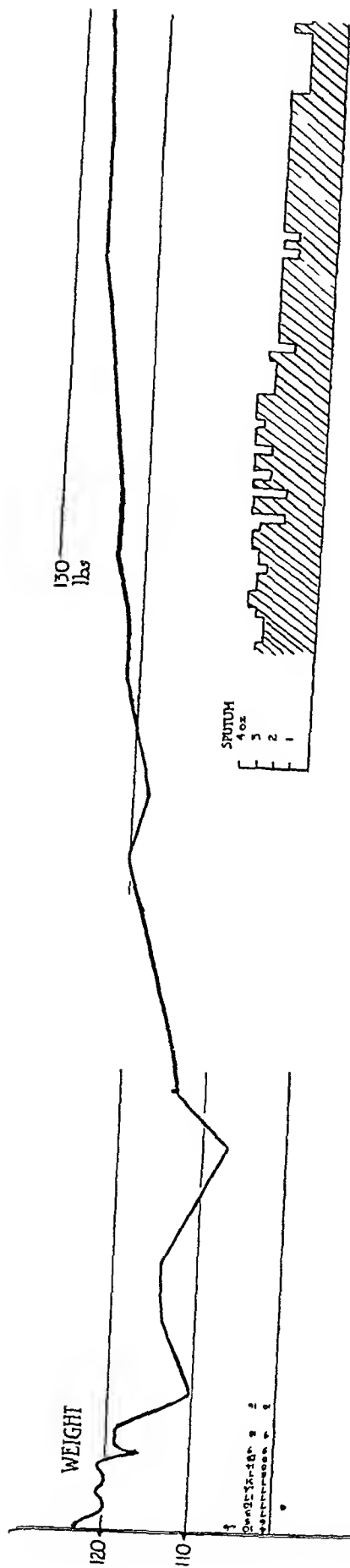
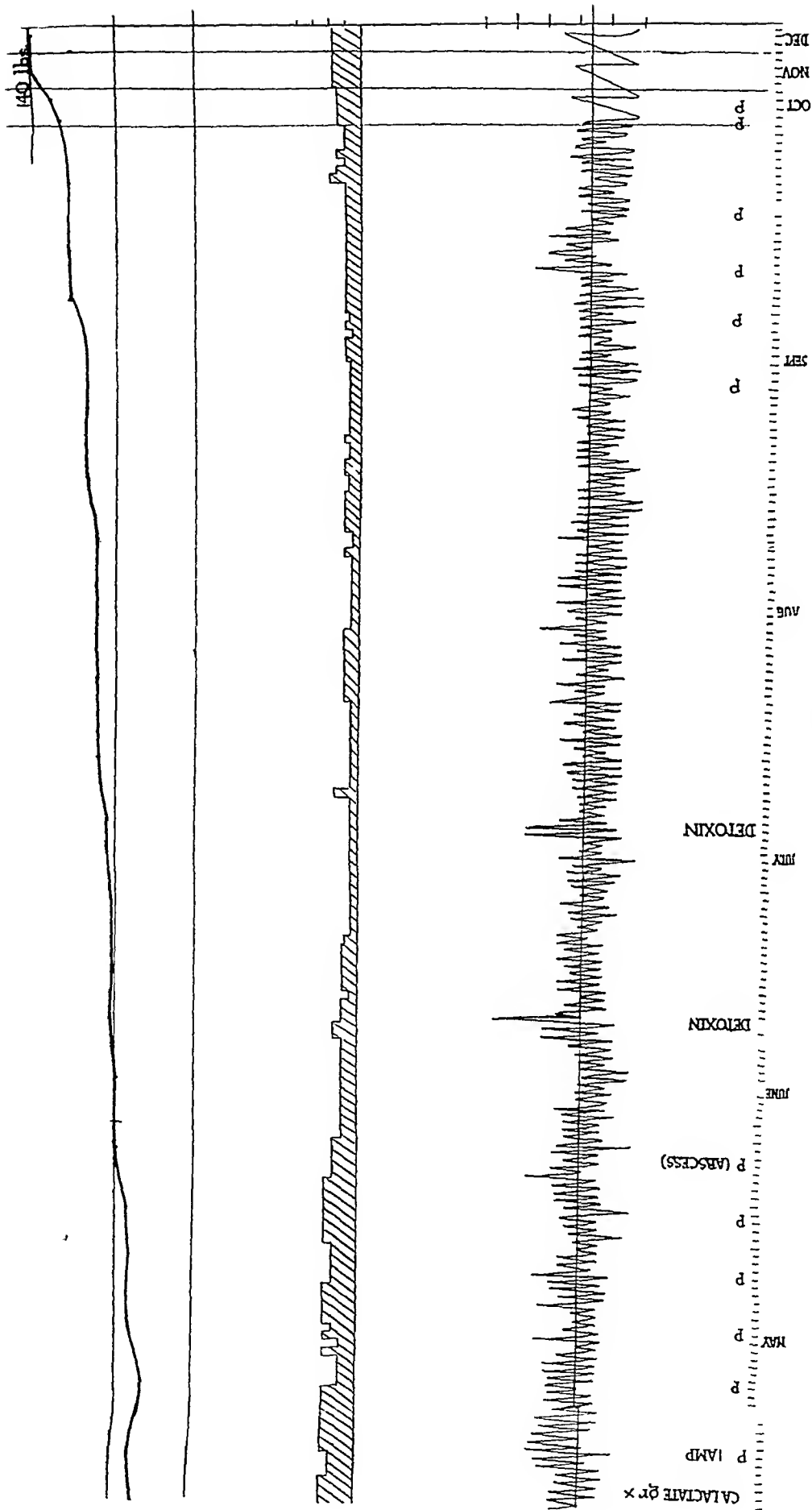


Chart 9—Clinical record in case 5 (far advanced pulmonary tuberculosis) The patient was treated with pituitary

Chart 9—Right



Anatomic Diagnosis—Ulcerative tuberculosis of the left upper lobe of the lung, chronic fibrous tuberculosis of the right upper lobe, bronchitis and bronchial pneumonia of the left lower lobe, fatty degeneration of the liver, cloudy swelling of the kidneys, ulcerative typhlitis, edema of the brain, recent thoracoplasty

Histologic Observations—Lung The wall of the cavity in the left upper lobe consisted of cellular granulation tissue with dilated capillaries. Toward the lumen the granulation tissue gradually passed over into cheesy masses. In the granulation tissue were many typical Langhans giant cells and a few young tubercles. Groups of foreign body giant cells contained peculiar calcified round bodies. In the outer portion, the wall was composed of fibrillar connective tissue with glandlike structure. Some of the arteries showed a marked thickening of the intima. In the left upper lobe, single tubercles were observed, composed of a cheesy center surrounded by dense scar tissue, with much anthracotic pigment. In the surrounding parts a few giant cells were assembled but there were no young tubercles. The lung tissue adjacent to the tubercles with the fibrous capsule contained many accumulations of lymphocytes.

Lymph Glands The lymph glands presented a diffusely calcified mass enclosed in a thin capsule of fibrous tissue. Near the capsule was a giant cell containing a calcified body. The other parts of the gland were hyperemic with much pigment.

Liver The liver cells contained small fat droplets. Near the center of the acini were granules of dark brown pigment besides the fat droplets. There were infiltrations of round cells in the periportal connective tissue.

Kidney The kidneys showed circumscribed areas of atrophy with hyaline glomeruli and round-cell infiltration. There was swelling of the epithelium of the convoluted tubules in the parts between the atrophic areas. Much fat was present in the lining epithelium of the ascending part of Henle's loops and the collecting tubules.

Spleen The spleen showed fibrosis of the pulp, and small follicles without centers.

Thyroid Gland The thyroid gland revealed medium-sized vesicles lined by flat epithelium and filled with homogeneous colloid.

VIII THE INTRACUTANEOUS REACTIONS TO INJECTION OF PHARMACOLOGIC SUBSTANCES DURING CHILL AND FEVER

In order to determine in some measure the extreme effects of vascular changes on the picture obtained when the intracutaneous pharmacologic tests are made, we examined the reaction in patients during the course of malarial inoculation, the determination being made before inoculation, during the time of chill and during the period of perspiration

In the chart, we have illustrated the relative sizes of the wheals and the flares at the sites of injection of epinephrine, morphine, thyroxin and caffeine

The wheal at the site of the injection of epinephrine during the time of the chill was somewhat reduced (on an average, from 10 to 15 per cent), while the flare was much more reduced. This was particularly apparent in patient 2. During sweating, the wheal regained its original size, and in two patients, the flare became much larger than under normal conditions

With morphine, too, during chilling, there was an apparent reduction of both the wheal and the flare, except in patient 4

With thyroxin, the wheal was increased during the time of the chill in two patients, but no flare appeared. With caffeine, there was an increase in the size of the wheal during chilling in patient 1, but a reduction in patient 3, so that the results were inconclusive

During chilling, the autonomic orientation is such¹ that the skin is distinctly sympathetic, while the visceral area is parasympathetic (these terms being used here to designate the state of the capillary bed). During chilling, too, epinephrine is being thrown into the circulation in increased amounts and apparently it accentuates the constriction manifest in the peripheral vessels

A reduction in the size of the wheals and flares at the sites of injection of epinephrine and morphine made evident during chilling might, therefore, justify us if we interpret reduced size of wheals and flares in general as indicative of an increased sympathetic peripheral tonus

On the other hand, the wheals at the sites of injection of thyroxin and of caffeine appeared somewhat increased during chilling in two patients, giving further evidence that the effects of thyroxin and caffeine are in direct contrast with the effect of epinephrine

¹ Petersen, W. F., and Muller, E. F. The Splanchnoperipheral Balance During Chill and Fever, *Arch. Int. Med.* 40: 575, 1927



A comparison of the sizes of the wheals and the flares at the sites of injection of the pharmacologic substances during malarial inoculation with their sizes under normal conditions

IX DISCUSSION AND DEDUCTION

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GENERAL CONSIDERATIONS

In the preceding group of papers, an effort has been made to correlate a number of measurable biologic reactions observed in normal persons and in patients, with each other, with clinical symptoms and with resistance to an infectious disease, i.e., tuberculosis.

In making the tests, we have sought to employ such as might presumably give information concerning the vegetative status of the individual, more particularly the status of the vascular system and the

epidermis We have sought, furthermore, to determine whether such a vegetative or autonomic status is related to the genotype or whether it is conditional (paratype, and therefore modified by preexisting and latent infection)

Incidentally, we have sought to determine what alterations in the tests that we have employed are indicative of increased or decreased resistance to tuberculosis and what therapeutic deductions might be drawn from such indications

In view of these particular interests, we cannot avoid a preliminary discussion of certain concepts concerning the vegetative status of the organism and the relation to the constitution in its widest sense

Study of the Individual Constitution—It is perhaps a natural swing of the cycle that is bringing medical interest back to an analysis of constitution and conditional reactivity The triumph of the "era of specific etiology" had completely overwhelmed every thought of constitutional differences in reactivity Obvious clinical experience was discredited and discarded when in conflict with experimental results from the animal laboratory Correction has followed, however, because of the obvious fallacy of the underlying method Precise clinical observation and animal experimentation brought incontrovertible evidence that neither in man nor in animals do like reactions necessarily follow like insults Even the physiologists and the pharmacologists have recognized that normal animals in deep anesthesia offer a test object totally different from sick patients

Recognition of the importance of differences in the host has come from the epidemiologist, as well Thus there are differences in reactivity of the skin and the mucous membranes, respiratory, as well as gastro-intestinal, which determine in a large measure one's liability to infection, as Arnold¹ has recently pointed out

The scientific study of the individual constitution has been under way from two important nonmedical sides The earlier anthropologist sought to formulate and define racial groups More recent studies have been broader and have sought to establish general types irrespective of racial grouping To this comes an added impulse through the modern study of heredity

Naturally, physicians have sought to make use of these two lines of approach and have applied them particularly to noninfectious diseases—in which "heredity" and "constitution" have never quite been denied But emphasis on anthropologic and genetic phases savors too much of predetermination to be wholly acceptable to the medical observer The conditional factors of environment, of tissue experience,

1 Arnold, Lloyd J Hyg 29 82, 1929

of preceding infection, of food, of light, of autonomic training (particularly of the skin), of climate—these must be of equal importance in variable susceptibility to infection, and resistance to one already established. However, many fruitful clinical observations and correlations have taken origin from these two sources. The literature is too large to be discussed, but a recent paper of Draper² and his co-workers is illustrative.

Views of Kraus, Bauer, Vetschuei, and Others—"Constitution" as a factor in the disposition to disease means different things to different investigators, depending on their particular interests.

We may, for instance, with Leo Loeb regard constitution as a synthesis and vital unification—the "individuality differential"—a view held by Martins and his school, as well, or go to the opposite extreme with Draper and examine everything from a purely anthropometric point of view. Bauer,³ on the other hand, discounted the value of the various anthropometric "indices" of this school, but nevertheless limited the term to the "genotype." Pfaundler stressed the importance of environmental (conditional) forces, i. e., the "paratype."

Many physicians have sought to group persons according to the presumptive reactivity of their glands of internal secretion and speak of the "hypophyseal," the "thyroid," or the "adrenal," type. Stein worked out a rather elaborate "glandular formula" and Pende⁴ theorized considerably in this direction. Of course, such a classification is attractive because it makes more easy the correlation of genotype and phenotype, the endocrine glands acting, presumably, in the modification of the inherited structure. With definite evidence of nervous control of the suprarenal (Cannon) and thyroid glands (Ascher⁵), the circles of biologic control become ever more intricate.

Kraus⁶ and his school, primarily clinical in orientation, stressed the idea of "personality," the term "Syzygiologie" having been coined for the new field.

The novelty of this point of view lies in the fact that it emphasizes the periphery of the organism, the region in which the metabolic processes are going on, and particularly the exchange between the cell and its environment, i. e., the membrane of the cell. As components of this system are to be regarded all factors that play into this intricate

² Draper, G., Allen, Grace, and Spock, Jane. *Studies in Human Constitution, Clinical Genetics*, J. A. M. A. **92** 2149 (June 29) 1929.

³ Bauer, J. *Klin. Wchnschr.* **8** 145, 1929, *Ann. Int. Med.* **2** 127, 1928.

⁴ Pende, Nicola. *Constitutional Inadequacies*, Philadelphia, Lea & Febiger, 1928.

⁵ Asher, L., and Pfluger, O. *Klin. Wchnschr.* **6** 1614, 1927.

⁶ Kraus, F. *Allgemeine und spezielle Pathologie der Person*, Leipzig, Georg Thieme, 1926, pt. 1.

exchange, either accelerating or inhibiting it, as for instance, water, the colloid electrolytes, salts, combinations of cations, the buffer system, hormones, definite endogenous and exogenous irritants and poisons, as well as the catalysts

The local and transient balance of this intricate mechanism is not determined only by the degree, the direction and the rapidity of the specific cell functions, but also by the degree and directions of the vegetative nervous irritability. The vegetative nervous system has the function of regulation—regulation in the sense that it determines to a large degree the distribution of the electrolyte reserves from one place to another.

In the logical development of this idea, Kraus came to the conception of a phylogenetically long established "Tiefen-person," that individualism of the most vital and most profound sort, a vital component of the constitutionally and primarily ordained protoplasm. This fundamental individualism is to be placed in contrast with the centrally organized and much younger cortical personality.

One of the great advances which lies in this concept of the constitution is, we believe, the fact that it emphasizes the impossibility of trying to coordinate isolated observations on both nervous systems (vegetative and central) without a proper regard for all the other factors of the vegetative apparatus. On the other hand, it is of use in the proper evaluation of the vegetative nervous system for all of our clinical problems. We shall refer repeatedly to the general idea.

Danielopolu⁷ also stressed the importance of the periphery, i. e., the terminal organ as the site at which the basic orientation of the individual is determined.

Perhaps, the simplest and most useful of medical points of view of constitution is that of von Verschuer,⁸ who defined it merely as "the relative (constitutional) status in the terms of resistance," stressing, nevertheless, that constitution (= *Korperverfassung* of Tandler = status,) is an organically fixed condition.

Bauer emphasized the importance of constitution in differentiating a group of biologically inferior persons—extreme variants from the normal—in adaptability, in vitality and in resistance. This, too, might seem a most useful concept for the physician.

He was content for practical purposes to group persons as

Slender	Normal	Heavy
(Dolicho, or asthenic type with small heart)	(Normotype)	(Brachy, or pyknic type)

7 Danielopolu, D. *Presse med* 31 649, 1923

8 Von Verschuer, O. *Klin Wchnschr* 8 769, 1928

The French have always associated the first group with lessened resistance to pulmonary infections, the latter group with gout, rheumatism, diabetes and arteriosclerosis

Sigaud made extensive use of the type terms muscular, respiratory, digestive and cerebral Kletschmer added the study of character in relation to constitution, the conscious reactivity being obviously a part of the general constitutional makeup To these and related classifications must be added those concerned chiefly with the functional status of the endocrine glands and finally the grouping of persons as primarily sympathicotonic or vagotonic

While we cannot review the recent contribution of Brown⁹ at great length we cannot but quote the pertinent conclusions that he has drawn from an elaborate and most convincing series of animal experiments that illustrate certain phases of constitutional resistance to disease Brown wrote

The elementary conception of constitutional variation and its relation to disease which I have attempted to outline involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions One need not know the function of a single organ in order to show that persons differ from each other in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic microorganisms It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by the changing conditions of life and that these changes in organic constitution are accompanied by variations in chemical constitution, all of which may be confined within the usual limits of normal, for they are normal It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity

In studying our material, we have disregarded all anthropometric factors and have used only the grouping of slender, normal and heavy, as based on the weight/length ratio

THE SLENDER (ASTHENIC) VERSUS THE HEAVY PERSON

It will be recalled that our two extremes based on such a classification showed, in general, the conditions set forth in table 1

Does such a classification have any necessary relation to the concept of "sympathicotonic type" or "vagal type?"

The Sympathetic Versus the Vagal Type—When we examine the ten persons with the extreme "sympathicotonic" reactions and the

⁹ Brown, Wade H Constitutional Variation and Susceptibility to Disease Arch Int Med 44 625 (Nov) 1929

ten with the extreme "vagotonic" reactions to epinephrine, as determined on the basis of the systolic reaction, we find the characteristics to be as shown in table 2. While the two classifications are by no means identical, we see that in both we deal with slender persons who have a

TABLE 1—*Characteristics of Slender Persons and Heavy Persons of Extreme Type*

	Slender * (Weight/Length Ratio 1.87)	Heavy † (Weight/Length Ratio 2.32)
Capillary permeability	0.63 greater	0.57
K/Ca ratio	1.81 lower	2.08
Sugar	69.50 lower	73.80
Basal metabolic rate	+10.00 greater	+7.00
Muscle reaction	2.38 greater irritability	3.48
Epinephrine pulse pressure	+12 increased effect	+8.00
CO ₂ -combining power	+58.5 slightly more alkaline	54.4
Cholesterol	210 lower	225
Reactivity of skin		
Resistance of skin to electric current	0.66 higher	0.28
Reaction to ice	21 longer	19
Kromayer light erythema time	2.21 longer	2
Epinephrine wheal	18.8 smaller	20
Morphine flare	14.8 smaller	15.8
Thyroxin wheal	12.2 larger	11
Thyroxin flare	4.8 larger	3.2
Caffein wheal	19.2 larger	18
Caffein flare	2.8 larger	2.4

* Microsplanchnic type: phthisic habitus, asthenic habitus, linear type of Stockard, Pende presupposes an increase in basal metabolism, predominantly "sympatheticotonic."

† Megalosplanchnic type: "apoplectic" constitution, pyknic type of Kretschmer, lateral type of Stockard, Pende presupposes increased cholesterol, increased potassium, relative alkalosis and chloride retention, predominantly "vagotonic."

TABLE 2—*Characteristics of Sympatheticotonic Persons and Vagotonic Persons of Extreme Type*

	Sympatheticotonic Group	Vagotonic Group
Capillary permeability *	69.1 increased	64.5
K/Ca ratio *	1.74 lower	2.04
Basal metabolic rate	+10.4 equal	+10.9
Muscle reaction	4 increased	23
Epinephrine pulse pressure *	+21.4 higher	-1.3
CO ₂ -combining power	54.6 lower	57.7
Cholesterol *	209 lower	218
Reactivity of skin		
Resistance of skin to electric current	0.41 equal	0.43
Reaction to ice *	23 longer	20
Kromayer light erythema time	1.72 shorter	1.95
Epinephrine wheal *	19.4 smaller	20
Epinephrine flare	9.4 larger	8.3
Thyroxin wheal *	12 larger	11.4
Thyroxin flare *	4 larger	3.2
Caffein wheal *	21 larger	19.2
Caffein flare *	2.6 larger	2.4

* The reactions indicated by (*) are identical in direction in both the "slender" and the "sympatheticotonic" groups.

low K/Ca ratio, an increased vascular reaction to epinephrine, lower cholesterol, somewhat less reaction of the skin to epinephrine, and a greater reaction of the skin to thyroxin and caffen.

The "slender" person in contradistinction to the heavy person has, furthermore, an increased basal metabolic rate, a more irritable musculature with a slightly lower CO₂-combining power of the serum, higher

resistance of the skin to electric current and a longer Kromayer light reaction time

The "sympatheticotonic" person in contradistinction to the "vago-tonic" person has no difference in the basal metabolic rate, less muscular irritability and a lower CO_2 -combining power, no difference in resistance of the skin to electric current and a slightly slower Kromayer light reaction time. The blood pressure is lower.

The Thyroid Type—If we now compare the extreme "thyroid" type, we also have a slender person (ratio 201) with increased capillary permeability (ratio 72) and increased basal metabolic rate (+48), no change in the K/Ca ratio, but an increase in the total serum calcium and potassium, the skin blister time is shortened, the ice reaction time is rapid, the resistance of the skin to electric current is low and the epinephrine wheal is small.

Pende¹⁰ assumed that the sympathetic type is characterized by a state of defense and aggression (raising of blood pressure and pulse rate, glycogenolysis, etc.) the parasympathetic type by emphasis on intestinal and reproductive phases (glycogen formation, congestion of sex organs, etc.)

Goldstein, too, stressed the general catabolism, irritability and aggressiveness of the sympatheticotonic status as contrasted with the euphoria and hypomaniacal status of the vagotonic psychopathic person.

In this country Cannon, in particular, has studied the sympathetic nervous apparatus and recently demonstrated the nonvital character of these nervous impulses. Even the medullary chromophil tissue of the suprarenal glands in contrast with the cortical portions of the glands—is apparently without vital importance. After bilateral sympathectomy, emotional excitement does not cause erection of hairs, consistent increase of blood sugar, polycythemia, relative increase in mononuclear cells or marked rise of arterial blood pressure. Sympathectomized animals are sensitive to cold, and having lost the means of conserving heat, they lose heat more rapidly than normal animals. The basal metabolism usually falls somewhat after sympathectomy, especially after the cervical portion is excised. Though seemingly unessential under "normal conditions," it is of great service at times of critical emergencies when it adjusts the internal organs of the body for the use of the mechanisms responding to external exigencies.

The experiments of Cannon¹¹ and his co-workers are of particular importance because they demonstrate that the humoral factors (particularly the chemical) of integration of vegetative phenomena, after all

¹⁰ Pende, N. *Riforma med. Naples* **41** 241, 1925.

¹¹ Cannon, W. B. *Science* **69** 502, 1929.

represent the older and underlying mechanism and must be considered in all of our medical problems, the nervous system being merely the more recent and less essential factor. As such, however, it may be the first to become disorganized and the first to give rise to clinical symptoms.

AUTONOMIC EQUILIBRIUM

The original concept of Eppinger and Hess of sympathicotonic and vagotonic types has unfortunately been so impressed on the medical mind that more modern developments dealing with the autonomic status of the individual have found but slow acceptance¹². It should be understood, as Ascher has so clearly stated, that the individual cells of the body are functionally distinct individuals, regulating their existence primarily through chemical means (this involves ionic, molecular, hormone and catalytic processes) and secondly, through nerve impulses, either central or vegetative.

Daniéopolu's Concept of Vegetative Tonus—Daniéopolu¹³ postulated three laws concerning reactions of the autonomic response which have an important bearing on the sympathicotonic and vagotonic conception.

In the first place, substances that influence one factor also influence the other, i. e., they are amphotropic. The evidence for this has been accumulating for many years, and the literature has been reviewed repeatedly¹⁴.

With eye pressure, Daniéopolu demonstrated that the impulses proceed along two pathways, along the parasympathetic to the heart and along the sympathetic to the gastro-intestinal tract. Daniéopolu concluded that the vegetative tonus is maintained by amphotropic factors: one, peripheral and humoral, the other centrifugal, from the sympathetic and parasympathetic centers. When the tonus of one side is increased, the other automatically follows.

In clinical medicine, we frequently see, however, an apparent overbalance of the one system. Daniéopolu believed that the preponderance depends on the intensity of the impulses. In pharmacologic experiments, we know the importance of the size of the dose of the autonomic drugs. The effect on an organ depends on the general vegetative status of the entire organism, i. e., a minimal dose of epinephrine, which in the normal person results in parasympathetic stimulation (i. e., slowing heart rhythm and lowering of the blood pressure) causes increased blood pressure and pulse rate in the sympathicotonic person, on the other

12 Editorial, Constitutional Vagotonia, J. A. M. A. **93** 1387 (Nov. 2) 1929

13 Daniéopolu, D. Klin. Wchnschr. **7** 1748, 1928

14 Pick, E. P. Arch. f. Physiol. **79** 183, 1920. Deutsche Ztschr. f. Nervenheilk. **106** 238 1928. Sollman, Torald. Physiol. Rev. **2** 479 1922.

hand, the dose which in the normal person causes increased blood pressure and pulse elicits a parasympathetic effect in the vagotonic person. These so-called paradoxical or inverted effects are, of course, well known. Finally, Danielopolu postulated a circular mechanism, the diagrammatic presentation of which we have reproduced.

Autonomic Equilibration and Increasing Amplitude of Response —

At this point, we should like to illustrate another fundamental phenomenon constantly met with in the study of autonomic regulation: first, the constant manifestation of the effort of the cell and the organ and the organism as a whole to maintain an equilibrium, disturbances of the balance being always followed by rhythmic and wavelike fluctuations in a direction opposite to the original change in status, second, the frequent manifestation of a progressive increase in amplitude in such rhythmic fluctuations following single impulses. We give charts for three typical experiments. The first shows the peripheral leukocytic fluctuations following bulbus pressure in the dog, the second, following irradiation of the skin. The third shows chemical fluctuations following a bacterial insult.

In a normal dog, a lymph fistula was made under local anesthesia. After reaction, bulbus pressure was maintained for seven minutes at the time indicated in chart 2. Peripheral leukocyte counts were made at frequent intervals, with determinations of lymph concentration, sugar, calcium and crepsin. The leukocyte count which reveals the fluctuations in the peripheral tonus (dilatation of vessels—leukocytosis, contraction, stasis, leukopenia) clearly indicates the rhythmic fluctuations of increasing amplitude initiated by this stimulus.

An almost identical picture is illustrated in chart 3. This dog had an exposure for seven and a half minutes to ultraviolet light applied over the abdomen, following recovery from incannulation of the thoracic duct under local anesthesia. It will be observed that the leukocyte curves show minor oscillations of increasing amplitude, with three chief periods of leukocytosis, the first 30 minutes, the second 75 minutes and the third 130 minutes, after the exposure. Calcium diminution occurs at approximately the same intervals.

In chart 4 we are able to illustrate an even more convincing picture with corresponding calcium fluctuations. In this case we deal with a bacterial insult. A pregnant dog was operated on under local anesthesia and an incannulation of the thoracic duct was made. After a period of observation following the operation, the continuous intravenous injection of a dilute suspension of *Bacillus coli* in saline solution commenced at 11:25 (first arrow on chart).

The curves at the top of the chart indicate the sugar level and the double line the K/Ca ratio (calcium level in black columns, potassium, in white columns).

The second group of curves indicate the rectal temperature and the volume of urine, the third, the lymph protein volume, the globulin per cent (in black) and the leukocyte curve. Inasmuch as the volume was sufficient to permit chemical analysis in five-minute samples, the actual fluctuation in the K/Ca ratio more accurately reflects the changes that occur in the tissues than has been possible in most of our other experiments.

It will be observed that the initial reaction was a slight increase in the calcium. A second and larger increase followed, reaching a maximum approximately sixty

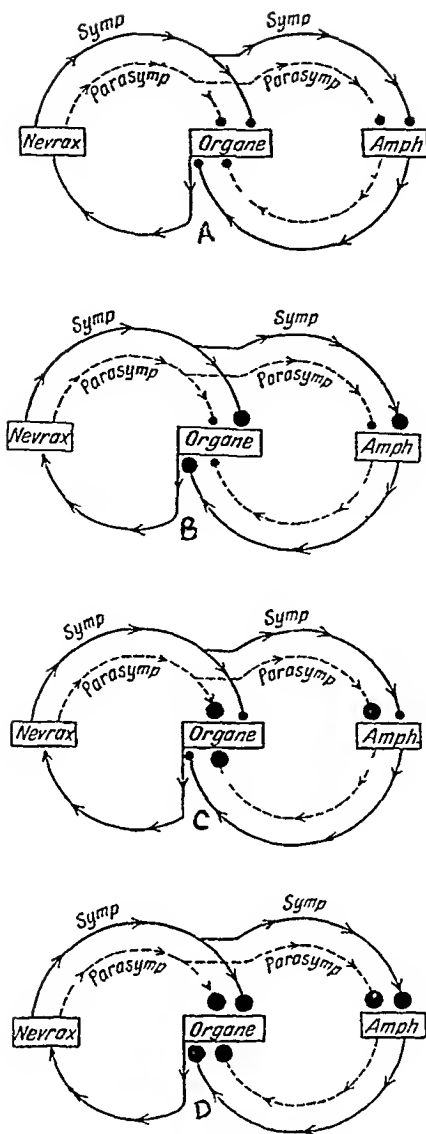


Chart 1—Amphotropic circular mechanism of the autonomic tonus and its variations (from Danielopolu, D Klin Wehnschr 7 1748, 1928) Diagram A indicates the normal status, i e., equal sympathetic and parasympathetic amphotropism indicated by the equal size of the black dots

Two factors are outlined the peripheral amphotropic humoral factor (involving calcium, potassium, epinephrine, choline, pituitrin, cholesterol, etc) keeping the sympathetic and parasympathetic nerve endings in a state of normal tone and maintaining a constant equilibrium The organ itself, through the centripetal connections, acts to maintain the proper tonus of the vegetative sympathetic and parasympathetic centers These centers again send centrifugal impulses via the sympathetic and parasympathetic tracts, which also act in maintaining tone in receptors This forms the primary circle, a secondary one is associated The glands of internal secretion, such as the suprarenal glands, which secrete amphotropic substances, have a dual vegetative innervation We also know from Loewi's work that the organs give off amphotropic substances during functional activity Grouped together, they may be called amphotropic secretory organs, in the charts they have been designated as "Amph" The impulses coming from the centers maintain a variable rate of activity in them, and this in turn regulates the peripheral factor

B, sympathetic status, the sympathetic dot is heavier

C, parasympathetic status, the parasympathetic dot is heavier

D, amphotonic status, both dots are heavier

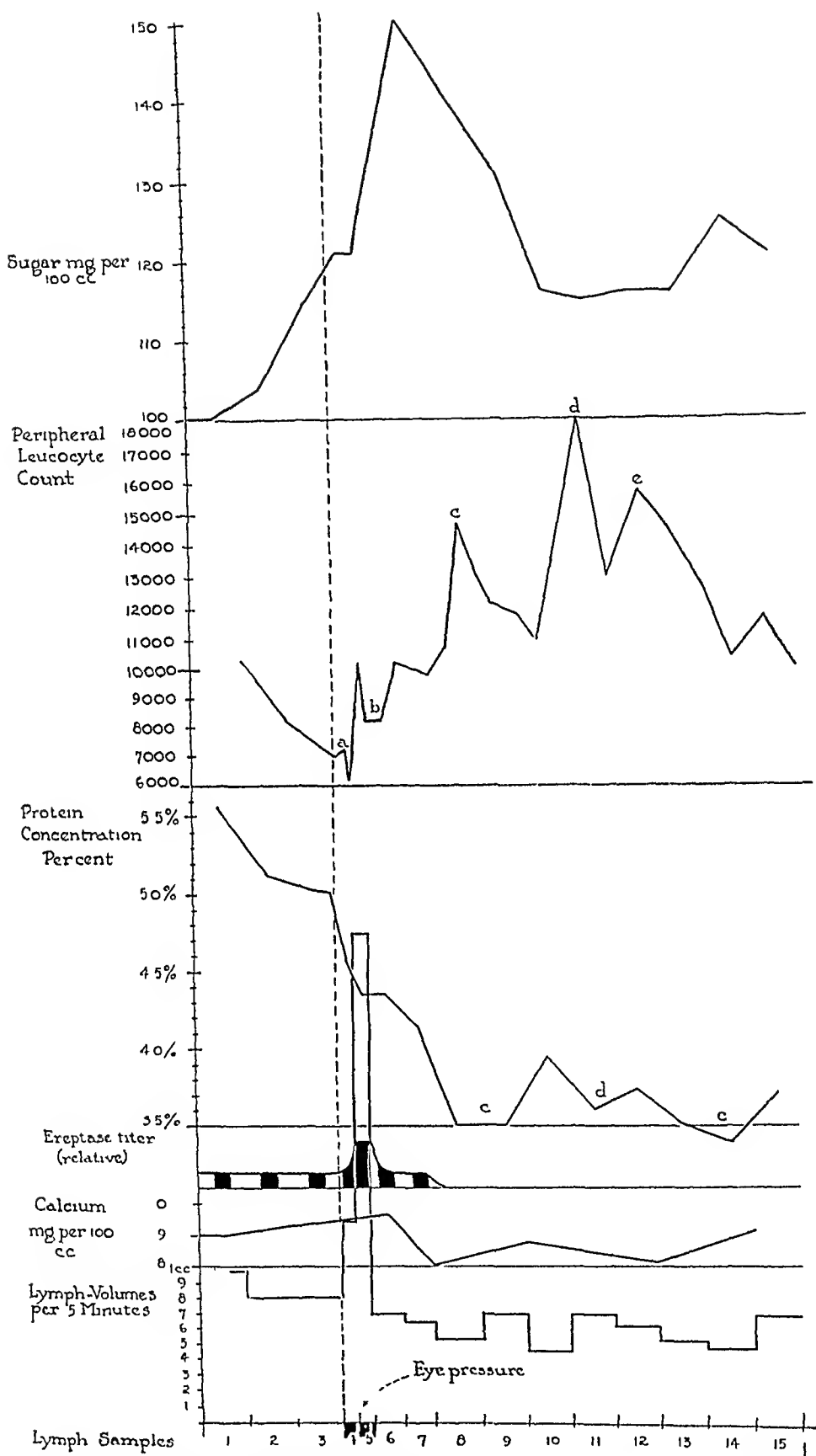


Chart 2 (exper 18) —Rhythmic tonus waves (leucocyte curve) of increasing amplitude following bulbous pressure in dog

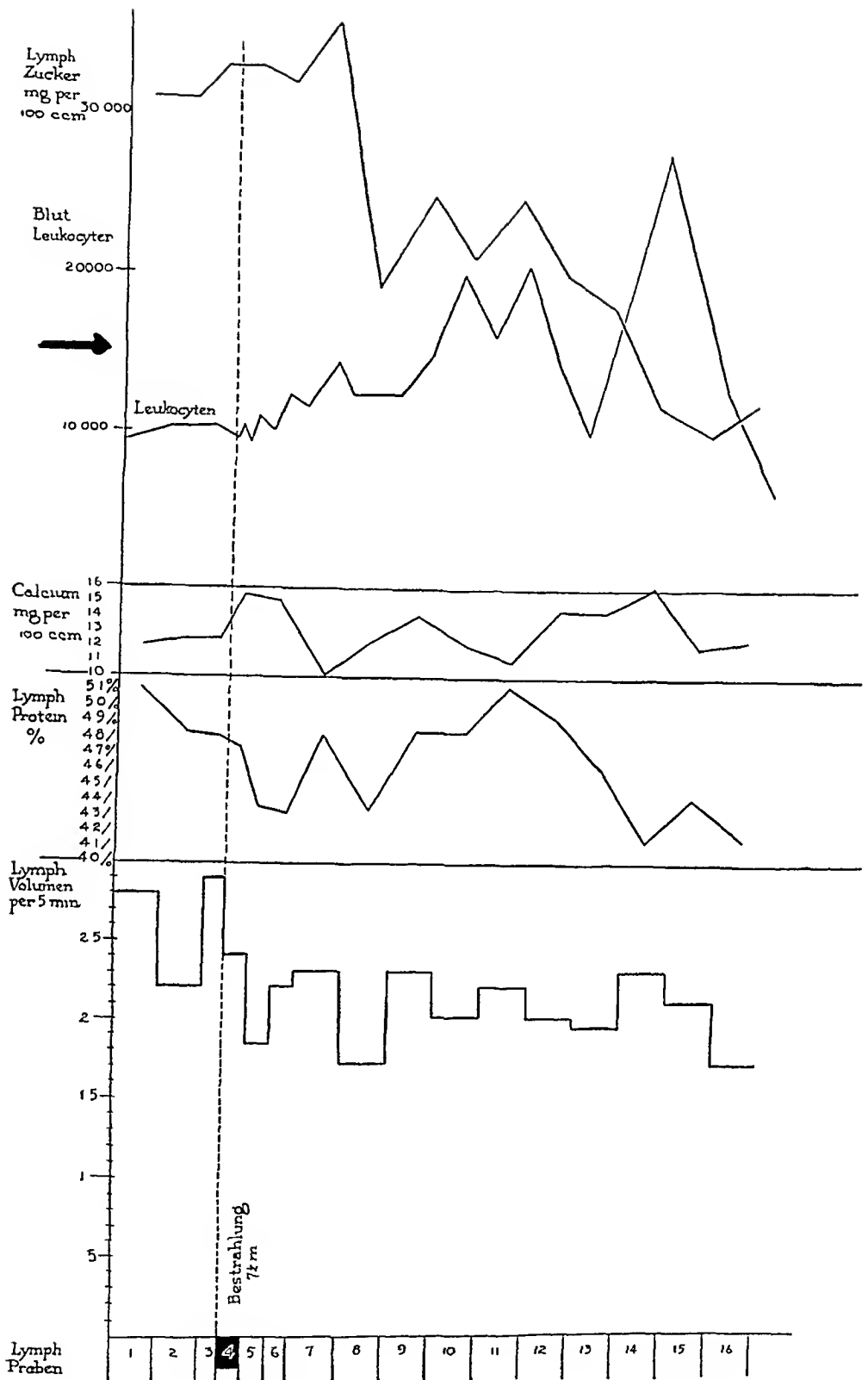


Chart 3 (exper 2) —Rhythmic tonus waves of increasing amplitude following ultraviolet irradiation (from Petersen, W F, and Von Oettingen, W F Veränderungen der Lymphe beim Hunde nach Quarzlichtbestrahlungen, Arch f exper Path u Pharmacol **128** 160, 1927)

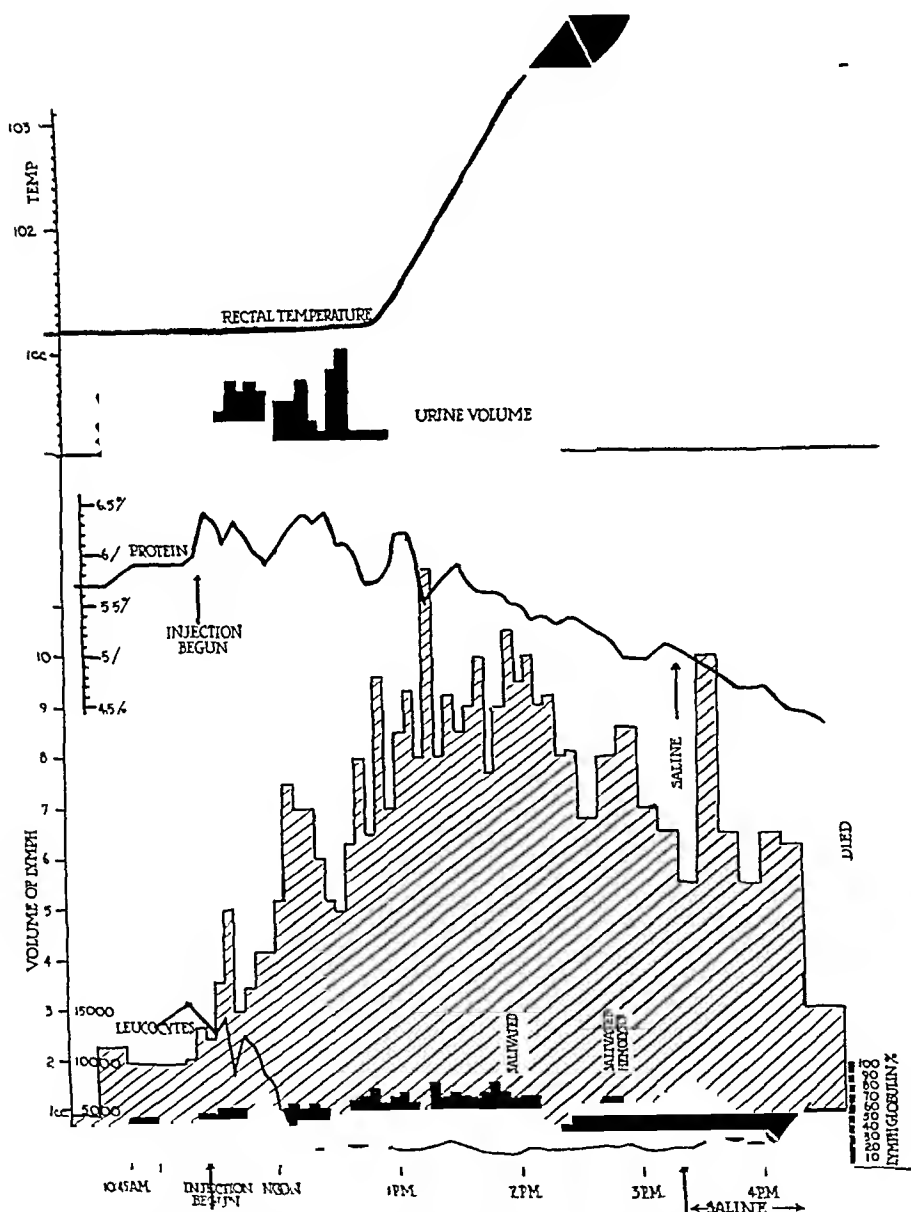
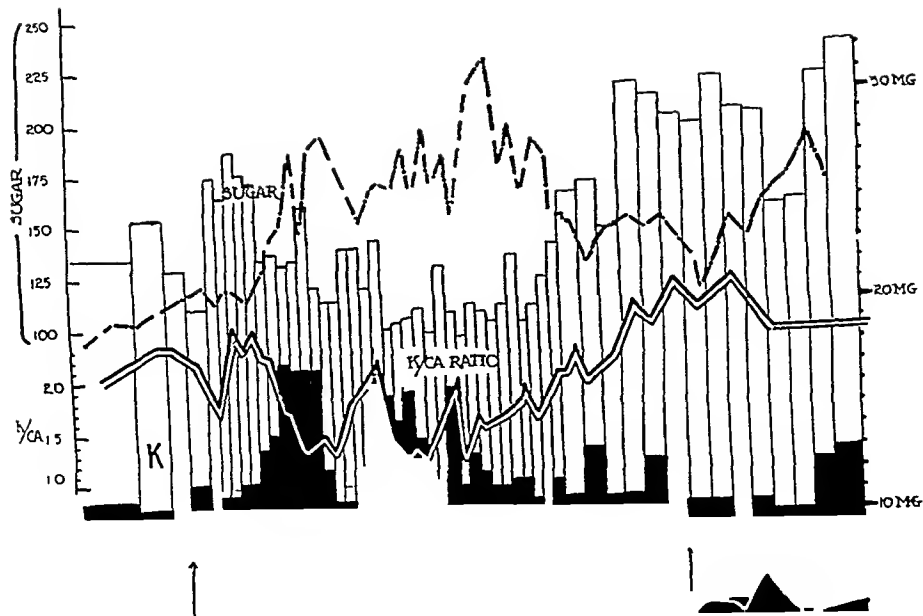


Chart 4 (exper 18)—Typical fluctuations in the calcium and the potassium of the lymph with continuous injection of *Bacillus coli* (from Petersen, W F, Milles, G, and Muller, E F *Ztschr f d ges exper Med* 60 336, 1928)

minutes after the beginning of the injection, another after two hours and the fourth after two and a half hours. After that, the effects were effaced by a large amount of potassium coming from the injured red blood corpuscles. These chemical changes find their counterpart in the sugar curve, the lymph volume and the concentration of lymph protein. In this particular experiment, the leukocytes do not show a corresponding fluctuation, because the upset of the normal vascular splanchnoperipheral balance is so great that the peripheral region becomes fixed in a sympathetic status.

These fluctuations of alternating periods of stimulation and inhibition which find their expression in changes in the K/Ca ratio, in the sugar level, in lymph volume and in protein alterations, etc., form part of the splanchnoperipheral balance which Muller and one of us have discussed in various papers.¹⁵

In view of the foregoing observations, it is to be remembered that not only the general and local autonomic tonus is to be taken into consideration when the reaction of tissue is studied, but that one is dealing with a constantly fluctuating, labile condition and therefore the time element and the particular phase will always modify the response of the tissue.

Obviously, stimuli reaching a cell or organ when on the up or down grade, or at the peak, as contrasted with the trough, of a wave, may bring about diametrically opposite physiologic reactions. Tinel, Santenaise and Laurent¹⁶ have made analogous observations in anaphylactic shock. They found that such shock always accelerates the preceding condition (status), and that then a reversal sets in. "Vagotonic" persons, for instance, have first increased excitability of the vagus, then a reversal sets in during which no further shock can occur. In the "sympatheticotonic," on the other hand, vagotonia is secondary, during which the patient is in a condition receptive to a new shock and to the continued effect of any circulating antigenic substance. With such a mechanism, one can more readily understand this reciprocal action of the autonomic tonus on shock and of shock on tonus.

Schilf's View of Autonomic Antagonists—Before leaving the more general aspects of this subject, we shall have to review briefly the views of Schilf.¹⁷ In line with the work of the Cannon school, Schilf pointed out that the older idea of a balanced nervous mechanism in the sense of a sympathetic-parasympathetic central antagonism, does not hold true for all tissues, there being a number in which only a sympathetic or only a parasympathetic innervation can be demonstrated. In the skin, for instance, we know of only sympathetic nerves for the sweat glands. Of greater importance for our problem, we know only of sympathetic nerves for the blood vessels. In only a limited region can parasympathetic (dilator) innervation be demonstrated, and the assump-

15 Muller, E. F., and Petersen, W. F. *Klin Wchnschr* 5 53, 1926

16 Tinel, J., Santenaise, D., and Laurent, O. *Bull et mém Soc med d hôp de Paris* 47 471, 1923

17 Schilf, E. *Klin Wchnschr* 6 29, 1927

tion that, because sympathetic fibers are vasoconstricting, vasodilatation must be accomplished by parasympathetic fibers, is at the least, not established, indeed is probably fallacious. Schulf frankly stated that this problem of nerve control of vascular dilatation is still an unsolved problem, an opinion which is apparently shared by Stohr^{17a}. He emphasized that the organs predetermine their own course of action, and that we should stress organ reactions rather than attempt to force through a rigidly conceived idea of a vasomotor mechanism which actually is controverted by experimental facts. Particularly, the pharmacologic interpretation has done much to confuse the picture rather than to clarify it. The effect of a nerve impulse to an organ depends on the state of the organ to which that impulse is delivered. Schulf emphasized this, in particular, because "sick" organs react differently from normal organs.

Schulf's real contribution is his analysis of the fact that apparently antagonistic autonomic reactions (sphincterbladder mechanisms, for instance) can occur without nervous control and that such reactions are, from a broader point of view, not antagonistic but synergistic. So, too, for example, the control of temperature regulation, which, according to Cannon¹⁸ is largely sympathetic. Here, again we are dealing with an apparent balance of sympathetic and parasympathetic impulses, apparently antagonistic, actually synergistic¹⁹.

A number of Russian physiologists and clinicians have reached conclusions similar to ours, among them Platoff²⁰.

To this comes a more recent possibility that the sympathetic nerves are not only efferent, but also afferent, and may play a considerable rôle in periodic differences in the sensitivity to impulses,²¹ and the contention of Viale²² that the increase in the heart rate that follows cutting the vagi, is really due not to the deletion of inhibitory impulses, but to the increased secretion of epinephrine that follows. The correctness of such experiments must, of course, be first determined.

The discussion up to this point has, we believe, shown that we cannot arbitrarily select any one of the numerous factors that are involved in tissue activity and make it alone responsible for the clinical alterations that we see in every day practice. We are seldom justified in trying to establish purely endocrine imbalances, much less are we

17a Stohr, Philip, Jr. *Mikroskopische Anatomie des vegetativen Nervensystems*, Berlin, Julius Springer, 1928.

18 Cannon, W. B. *Tr. A. Am. Phys.* **44** 41, 1929.

19 Petersen, W. F., and Muller, E. F. *The Splanchnoperipheral Balance During Chill and Fever*, *Arch. Int. Med.* **40** 575 (Nov.) 1927.

20 Platoff. *Russk. Klin.* **5** 3, 1926.

21 Forster. *Schless. Gesellsch. f. vaterland. Kultur*, Breslau, *abst. Klin. Wchnschr.*, Feb. 1, 1929.

22 Viale, G. *Boll. d. Soc. ital. di biol. sper.* **2** 54, 1927. Smirnow, A. J., and Schinokj, W. F. *Ztschr. f. exper. Med.* **55** 24, 1927.

justified in trying to establish a purely nervous imbalance. We might do best by following Bergmann and speaking of certain groups of patients as "vegetatively stigmatized," and we should definitely discontinue regarding only the readily observable smooth muscle reactions as criteria of systemic autonomic change. The smooth muscle, with its tonus, represents primitive contraction, the twitch of the voluntary muscle appears much later. But this tonus requires little oxygen, it is a vegetative phenomenon regulated by the bio-electric (ionic) means. Later, we superimpose vegetative and voluntary nerves, as well as the specialized amines and vegetative poisons, epinephrine, histamine, choline, etc., which can obviously act, as Langley suggested, directly on the cell membranes by changing colloidal structure, not necessarily on the nerve endings.

And if, in clinical parlance, we continue to use the term "sympathicotonic" or "vagotonic" in lieu of the broader one of "autonomic dysfunction" or "vegetative stigmatism," we should have clearly in mind the many reservations which we have indicated.

The entire field of the "autonomic nervous system" has been thoroughly reviewed by Kuntz,²³ or one may consult the older book of Muller.²⁴ The more clinical "Vagotonies, Sympathicotones and Neuritones" by Guillaume²⁵ also offers much detailed information.

THE CHEMICAL EQUILIBRIUM

In the preceding discussion, we have traced the changes which have taken place from the original concept of functionally antagonistic sympathetic and vagus centers with resulting sympathicotonia and vagotonia, to the present view with its emphasis on the autonomic status of the periphery. In the peripheral organ, we have already seen the presumptive influence of its milieu, its hormone content, its chemical equilibrium, etc., in determining local autonomic tonus and have also made note of the possibility of the effect of remote organs on such local tonus.

Rôle of Calcium and Potassium and the H-Ion Concentration—The interest in the chemical phase goes back to the work of Jacques Loeb, who first emphasized the importance of the ions, particularly of calcium and potassium ions, in the control of cellular functions. The more recent and intensive cultivation of the field, particularly the application to clinical problems, comes from the school of Krause. Thus, Zondek,²⁶

23 Kuntz, Albert. *The Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1929.

24 Muller, L. R. *Die Lebensnerven* ed 2, Berlin, Julius Springer, 1924.

25 Guillaume, A. C. *Vagotonies, Sympathicotones and Neurotonies*, ed 2, Paris, Masson & Cie, 1928.

26 Zondek, S. G. *Klin. Wchnschr.* 2: 382, 1923, 3: 707, 1924, 4: 905, 1925, *Die Electrolyte*, Berlin, Julius Springer, 1927.

after calling attention to the activity of ions on colloids in influencing their dispersion, hydration, etc., stresses the fact that two balances are of greatest physiologic importance the H-ion concentration and the K/Ca ratio

In general, we may accept the following

With cellular activity, the calcium concentration of the cell membrane is diminished. Calcium leaves the cell, and there is a relative increase in potassium in the cell. The cell is more permeable, the protein becomes hydrated.²⁷

From this stage of activity, as one pole, the opposite extreme, of rest, is reached, with apparently a relative increase of calcium at the cell surface, relative impermeability, dehydration, etc. Calcium and potassium concentrations are therefore indicative of the swing of the pendulum of cellular activity (Osterhout,²⁸ Lillie²⁹)

These changes are cellular changes. They may be initiated by external impulses, a nerve impulse, for instance, the tone, however, will depend on a mechanism such as Danielopolu described. The concentration of either calcium or potassium in the serum may mirror the cellular change, but it must be clear that the serum levels do not necessarily change the reactions of the cells. The alteration of ionic concentration may ultimately bring about an abnormal vegetative reaction, but we may, and frequently do, find unipotential autonomic reactions without a corresponding consistent blood chemical picture.

The temptation is great to associate certain effects brought about by the increase of ionic concentration with definite autonomic nerve tonus, for instance, calcium with sympathetic effects, and potassium with vagus effects.

This association has been an outcome largely of clinical observations with injections of epinephrine hydrochloride. In the analysis which we present of our material on the basis of the epinephrine reaction, we have clearly shown that, while our outstanding "sympatheticotonic" persons had a lower K/Ca ratio (i. e., have relatively less potassium) than the outstanding "vagotonic" persons, there are many exceptions to the rule. But the fact that we find many exceptions to the rule, as did Brems,³⁰ and the fact that Jendrassik and Czike³¹ could find no constant correlation at all between the reaction to epinephrine and the K/Ca ratio do not for a moment vitiate the importance of the ion balance for these autonomic alterations. We must not forget that the epinephrine

27 Zondek, S. G. *Biochem. Ztschr.* **132** 362, 1922

28 Osterhout, W. J. V. *Injury, Recovery and Death in Relation to Conductivity and Permeability*, Philadelphia, J. B. Lippincott Company, 1922

29 Lillie, Ralph. *Protoplasmic Action and Nerve Actions*, Chicago, University of Chicago Press, 1923

30 Brems, A. *Acta med. Scandinav.* **66** 207, 1927

31 Jendrassik, L., and Czike, A. *Klin. Wchnschr.* **6** 1521, 1927

acts on the cell membrane—peripherally, the reaction of the cell depends on its status, tonus, i.e., on the ionic condition of its surface membrane. The relative ionic concentration of calcium and potassium in the adjacent cell fluids, quite apart from the blood, is only of secondary importance. Furthermore, all of our results and those of numerous others are estimated as total calcium and probably give a picture far different from the actual ionic calcium available.

Confusion of the Terminology Involved—We must keep in mind, furthermore, that cell membranes are interposed between the cell protoplasm and the blood stream.

With a Donnan equilibrium here established, the amount of non-dialyzable ions combined with protein on both sides of the membrane and the total amount of protein becomes of greatest importance.³² We have shown by actual experiments (see chart 4) that with cell stimulation, calcium is liberated from the cell protoplasm and potassium there increased—corresponding to the time of vascular dilatation of the organ and therefore to a presumptive vagotonic status of the capillaries and tissues. This would mean that if we now use the term “vagotonia” as denoting a condition of tissue activity with capillary dilatation and increased permeability, then the blood stream should contain more calcium and relatively less potassium.

Actually, Kylin³³ found the “vagotonic” person, as clinically defined, to have more potassium and less calcium (higher K/Ca Ratio), and we, too, in using this clinical classification, can but confirm this.

Dresel³⁴ assumed that the blood of the “vagotonic” person is more alkaline and contrasts the resulting ionic states as follows:

<i>Vagotonic Status</i>		<i>Sympatheticotonic Status</i>	
Tissues	alkaline little calcium-colloid, much potassium-colloid	Tissues	acid much calcium-colloid, little potassium-colloid
Blood	alkaline little ionized calcium, much bound calcium, little potassium	Blood	acid much ionized calcium, little bound calcium, much potassium

Accordingly, the “vagotonic” person should have a low K/Ca ratio, the physiologic effects being modified, however, by differences in ionization.

What we are actually facing here is merely a difference in definition. The clinical grouping of “vagotonic” does not define a person whose metabolism is increased and whose capillaries are permeable and dilated. This we should expect if in the vasomotor definition “dilatation” is synonymous with the “vagus effect.” On the contrary, the clinically

32 The capillary endothelium is permeable for proteins when stimulated.

33 Kylin, E. *Deutsche Arch f klin Med* **149** 354, 1925, *Die Hypertonie-krankheiten*, Berlin, Julius Springer, 1926.

34 Dresel, K. *Klin Wchnschr* **1** 1601, 1922, *Klin Wchnschr* **3** 311, 1924.

"vagotonic" person has a lower rate of metabolism and less permeable capillaries Dresel was correct in theory, Kylin in practice We can illustrate this further in the chemical changes of sleep³⁵

Here we deal with a "vagotonia," even in decerebrate animals There can be no doubt about the general condition of tissue rest, during this time, calcium diminishes in the blood and increases in the tissues and the potassium values show the reverse The greater frequency of attacks of asthma and angina pectoris, the occurrence of pavor nocturnus, Pende ascribed to the vagus preponderance at night

Clinical Grouping of Vagotonic and Sympatheticotonic Persons—We have discussed this at some length to bring out the fallacy of our present classification of "sympatheticotonic" and "vagotonic" It should be given up, unless we are clearly cognizant of the various implications

When we have spoken of the sympathetic status, we have always indicated the state of tissue rest contracted vessels, calcium accumulation, dehydration³⁶ When we have spoken of the parasympathetic status, we have indicated the state of the tissue with dilated capillaries, tissue activation, calcium dissimulation, hydration When we have used the terms "sympatheticotonic" and "vagotonic," we have designated the clinical states as commonly interpreted

And this brings up another apparent inconsistency When smooth muscle contracts, the obvious inference is that the muscle tissue is active (it may contract, of course, with either sympathetic or parasympathetic stimulation), but actually during contraction the capillaries are also contracted, their endothelium is less permeable, metabolic processes are slowed, less energy is supplied With relaxation comes dilatation of the vascular bed and increased permeability Relaxation must, therefore, if we wish to be consistent, be the period of metabolic activity, i e., the parasympathetic status in the sense that we have used it

Now, it happens that when epinephrine is injected in small doses, the blood vessels dilate and the endothelium becomes more permeable It is a true parasympathetic status of the tissues With larger doses, the vascular musculature contracts, and the endothelium becomes less permeable These are direct cellular effects and take place presumably without nervous mediation This is a true sympathetic effect But the many other effects initiated at the same time by the large dose of epinephrine result in a most complex picture

35 Fischer, H Biochem Ztschr 193 169, 1928

36 If the sympathetic status with contracted vessels occurs for a long period of time with a resulting stasis in the capillaries, it is possible that the cellular metabolism of the region will show a condition far different from "rest," i e., rather an asphyxial stimulation Such states may presumably occur in the peripheral tissues during a chill

Of course, Zondek³⁷ was careful to state that the vagus effect is like the potassium effect, he never insisted that the two are identical, although, in general, it is assumed that the nerve impulse makes use of the ions in upsetting the membrane equilibrium. With this consideration, one can understand why in certain clinical conditions—urticaria, for example—the calcium level may be normal and yet the administration of calcium be, at times, useful, at other times, without effect. We can understand why the level may be constant—and it is one of the most firmly held of the balances, as Kroetz³⁸ has shown, with a negative balance, i e, cells may be losing calcium, but the level remains the same, as Aub³⁹ and his associates have so clearly demonstrated in exophthalmic goiter. And we can understand why the level may be low in the blood, while the relation in the cell membranes is at its proper level.

Rôle of Cholesterol—There seems to be some basis for the belief that cholesterol is involved as an intermediary in the ionic autonomic mechanism that we have been discussing,⁴⁰ and here again we are dealing with a confusion resulting from the presumable effects of cholesterol as a component of the cell membrane and cholesterol free in the blood stream. It is, of course, possible that an increase in the cell membrane can be present at the same time that we have an increase in the blood stream. The possibility also exists that with an active exchange going on between the two, high membrane content may be associated with low plasma content and vice versa. Just as with the ionic balance, the membrane relations present great complexity, with innumerable physical and chemical differences, free and saponifiable forms and the ability of the blood proteins to form protective colloids all influencing the ultimate balance. Mjassnikow⁴¹ definitely associated the increase in blood cholesterol with hyperasthenia, not only in the apparently normal condition, but in the associated diseases, of this constitutional type, i e, gout, obesity, hypertonia, asthma, hay fever, gallstones, etc. This cholesterol increase appears to be true for our "heavy" group, as well.

But Dresel and Sternheimer⁴² definitely placed cholesterol in the sympatheticotonic group, counterbalanced by lecithin as a parasymp-

37 Zondek, S. G. *Klin. Wchnschr.* **6** 1951, 1927, footnote 26, second reference.

38 Kroetz, C. *Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong.* **40** 91, 1928.

39 Aub, J. C., Bauer, W., Heath, C., and Roper, M. *J. Clin. Investigation* **11** 97, 1929.

40 Westphal, K. *Ztschr. f. klin. Med.* **101** 545, 566, 584 and 603, 1925.

41 Mjassnikow, A. L. *Ztschr. f. klin. Med.* **105** 228, 1927.

42 Dresel, K., and Sternheimer, R. *Klin. Wchnschr.* **4** 816, 1925.

pathetic agent Glaser⁴³ discussed some of the relations in arteriosclerosis and found, as had Wacker and Hueck,⁴⁴ that the injection of epinephrine hydrochloride increases the amount of cholesterol in the serum. A complete discussion of the literature would be superfluous at this time. We merely mention the probable rôle of these lipoids in the chemical and physical equilibrium that is involved in the autonomic background.

THE SKIN

Its Autonomic Importance—Among the vegetative organs concerned with our immediate relation and adjustment to the outside world, none is of greater importance than the skin, it is unfortunate that it has been largely ignored by the physiologist, perhaps, because in his preoccupation with the experimental animal, he has failed to realize how far different the human skin is in its reactivity from that of any of the lower animals, perhaps because he has regarded the skin merely as a protective mechanism—the “overcoat” with which Engman has chided the dermatologists for their narrow point of view.

As a matter of fact, the skin is the reactive membrane for the whole organism, just as the cell membrane is for the individual cell, and with almost as many important and sensitive receptors and reactive possibilities. Clinical observation has always recognized the interrelation of the skin and the deeper tissues. The so-called antagonism of visceral and skin tuberculosis and syphilis is one example. So, too, is the protective immunity established by the exanthems, and the tradition that a good reaction of the skin protects against internal complications in the same group of infections is established folklore. More recently, the rôle of the skin in allergy and the therapeutic possibilities incidental to stimulation of the skin have raised the clinical interest and aroused considerable investigative curiosity. Muller and Delbanco⁴⁵ developed the idea of the skin as a vegetative sense organ and in line with von Groer⁴⁶ emphasized the skin as a mediator of autonomic regulations by virtue of both its chemical and its physical potentialities.

As is well known, the latitude of the adaptability of the skin to an insult or to a change in environment is great, must of necessity be great, because on it depends the life of the whole organism.

We should therefore like to develop the subject of the importance of the skin and its autonomic tonus in more detail and shall use bacterial invasion as an example of the effect of an abnormal external insult.

Local Resistance—The sum total of the processes involved may vary from the normal physiologic responses, or what may be termed

43 Glaser, F. *Klin Wchnschr* 6 2377, 1927

44 Wacker, L., and Hueck, W. *Munchen med Wchnschr* 60 2097, 1913

45 Muller, E. F., and Delbanco, E. *Dermat Wchnschr* 87-1348, 1928

46 Von Groer, F. *Klin Wchnschr* 6 96, 1927

"local tissue resistance," all the way to the severe inflammatory reactions elicited when certain organisms or biologically active toxic substances penetrate the superficial layers. The human skin, as we have pointed out, is much more reactive both specifically and nonspecifically than the skin of other animals.

The inflammatory reaction differs in degree from the normal physiologic response, the direction of the change is apparently uniform at the onset in both cases. Both the "local resistance" of the normal and undamaged tissue and the inflammatory resistance depend to a marked degree on the preexisting vegetative status of the tissues.

In order to maintain local resistance of the tissue an unaltered function of the cellular elements is the prime requisite, the second is an undisturbed replacement of the energy requirements during the course of normal metabolic processes. This involves a definite orientation of the autonomic apparatus of the involved tissue, so that the full development of tissue function and energy supply can be maintained.

Certain cells, particularly those that are to some extent free from cell complexes and organs (reticulo-endothelium and the resting wandering cells of Maximow), are more independent in their adaptability to changes in the environment insofar as they seem less subject to the influences which are operative when cell groups are involved.

On the other hand, in the organized tissues, every reaction of one organ involves more or less directly certain fundamental correlations with all the other organs and tissues. Brown's⁹ work makes this interrelation evident. Remote organs, under conditions of stimulation, may then act either as accelerators or inhibitors of the function of other organs, whereby the adaptability of a remote zone may be enhanced or retarded.

The law of Dastre and Morat and our own experiments with the splanchnoperipheral balance of the organs show this clearly. If, for any reason, we observe a sudden increase of activity of the abdominal organs with increased vascularity of the region, there is not only a diminished amount of blood in the peripheral vascular bed, but also a diminution in the functional capacity of the peripheral organs associated with synchronous contraction of the vessels.⁴⁷

We have already touched on the autonomic vascular mechanism involved, in connection with the paper of Schifl. We shall here limit ourselves to the question how far such alterations (which are constantly occurring under physiologic conditions) influence the organs and tissues.

47 Fremont-Smith, F., Morrison, L. R., and Makepiece, A. *Proc Am Soc Clin Investigation*, May 6, 1929, abstr., *J Clin Investigation* 7:489, 1929. Smith, Morrison and Makepiece have recently made observations on the capillaries during chill and find a complete stasis in all visible capillaries due to the constriction of the terminal arterioles.

with a possible loss of the local resistance of the tissue and predisposition to disease

Herpes and Splanchnoperipheral Balance—On the skin, in the nasal mucous membrane, and in the gastro-intestinal mucous membrane, pathogenic organisms live without further penetration, that is, until at some time a slight trauma, a "cold" or some other indisposition leads to local infection. With mechanical injury and its obvious disturbance, the lowering of the resistance of the tissue is easily understood. It is much more difficult to understand the other types of susceptibility, the appearance of a labial herpes for instance, with a sudden onset of fever. We know its pathognomonic interest and the enormous spread occasionally seen in association with the chill of an infection with *Bacillus coli*, we also know the nasoparasitic character of herpes virus.

The ubiquitous virus previously present in the adjacent surface of the skin suddenly penetrates the superficial layers and, from the clinical point of view, becomes virulent at the time of systemic reaction incidental to the generalized disease. The virus, having once penetrated, meets with further resistance in the form of local inflammation, the intensity of which is usually sufficient to check the further spread.

This picture is a typical example of the transition of a previously latent organism to full virulency as the result of the failure of local resistance of tissue. The question as to the cause of such failure with the onset of the chill and high temperature is of far greater interest than that involved in the mechanism of the infection of the pelvis or uterus with *B. coli* in septic abortion. Other herpetiform invasions are apparently related to similar processes—the herpes infection of the skin in certain periods of the menstrual cycle, and in certain persons during acute indigestion, etc.

The cause is always the same. A sudden and intense increase of activity in the splanchnic region involving marked increase in the vascular bed and increase of the secretory function reflexly involves a change in the peripheral tissues. The change includes a diminution in the size of the vascular bed and a reduction of cellular activity. The periphery becomes less capable of reaction to external stimuli for the reason that reactions which under normal conditions are associated with increased vascularity and increased metabolic cell processes are either diminished or do not make their appearance.

A second possibility must be considered. The stasis of the peripheral capillaries may be of sufficient duration to bring about injury of the more superficial epithelial cells—cells that normally are undergoing necrobiosis. This dysfunction incident to the stasis may be sufficient to account for the penetration.

Such alteration of the distribution of the blood takes place in all conditions associated with fever. A similar redistribution in the vascular

bed together with an increase of the secretory function of the stomach and other large glands of the abdominal region occurs in varying intensity during the menstrual cycle, during migraine and even during digestion, more evident in certain persons, when we see it as part of the "Widal hemoclastic crisis"

The cause of this abdominal splanchnic dilatation may vary in individual cases, but the reaction of the organs and the vessels in the splanchnic region is fundamentally the same. It is unidirectional, and it is associated with peripheral constriction made apparent in the pallor of the skin, with headache, with nausea, etc. In the chill of an infection with *B. coli*, one can observe the most intense form of this splanchno-peripheral change. The enormous increase in activity of the liver which results from the systemic invasions is associated with a decreased flow of blood at the periphery and a diminution of all peripheral cellular function. It is this latter change which is of the greatest practical importance.

Heat radiation and sweat formation are clinically familiar to us. Their inhibition, even if transient, is part of the mechanism that causes fever, because the dissipation of heat produced by the increased activity of the splanchnic organs is thereby checked. Only when, with gradually diminishing activity of the liver, the correlated inhibition of the autonomic functions of the skin is lessened, does the temperature begin to fall. During the menstrual cycle, similar conditions may prevail even though the clinical symptoms are less apparent. Here, too, one finds minor fluctuations of temperature that have the same physiologic basis, though here without infection.

Local tissue resistance, which is most impressive in the skin, is subject to the same inhibitory influences. Reactions of the skin associated with increased resistance to infection are hard to recognize. It is true that our clinical experience indicates that a skin or a mucous membrane with good circulation is less apt to become infected, and that healing takes place more rapidly under such conditions. This might be apparent, too, from the relative freedom of the exophthalmic patient from infections of the skin.

Inhibitory influences on the skin, with diminution of its autonomic adaptability, also become apparent only when every day demands are not met in the normal fashion, for example, when one has a virus present and finds that with lowering of the local tissue resistance, the virus is enabled to penetrate into the deeper tissues.

It is of secondary importance whether such an inhibition takes place primarily through nerve impulses, through alteration of the metabolism or through endocrine alterations which secondarily lower the resistance toward the infections.

We ⁴⁸ have previously noted definite autonomic influences on the skin of women during the menstrual cycle. In the absence of a potential virus on the skin, these alterations are clinically innocuous because practically, one is dealing only with a susceptibility toward infection. Only when one is dealing with a potential infection, as in persons harboring the herpes virus, does the periodic depression of resistance become apparent.

Respiratory Tract—In the nasopharynx, similar autonomic influences become apparent. In chill and in high fever, the mucous membranes of the mouth and the nose are dry because the cell functions of the mucous membranes are definitely depressed or inhibited. The coated tongue is a manifestation of the same influences.

Glands and mucous membranes are in themselves uninjured, it is only their functions which are diminished during the time of fever. Despite urgent need and mechanical stimulation through chewing and sucking and contact with food, the formation of saliva is inhibited because of the vegetative contraction of blood vessels as well as the vegetative inhibition of the cell functions. The same condition holds true for the hunger sense. The diminution of contractions that we ⁴⁹ have demonstrated for the stomach during this time is part of the picture of diminished appetite (the opposite vegetative orientations of salivary glands, mucous membranes and tongue, on the one hand, and of stomach, liver, etc. on the other, are particularly marked in these cases, as we have shown previously). The stomach during this time is under a condition of stimulation which leads to a considerable secretion of a strongly acid stomach juice.

Other infections of the mucous membranes besides herpes are well known during fever, for instance, the inflammatory reaction of the upper part of the respiratory tract, as well as of the conjunctiva. Such inflammatory reactions are by no means to be regarded as part of the primary infection, but are merely manifestations that these tissues for the time being have lost their resistance either partially or entirely, resistance which under normal conditions would be more than able to cope with every day irritations. Here for instance, could be mentioned the conjunctivitis occasionally seen with the flare-up of a localized pulmonary tuberculosis, so characteristic that it may be regarded as a distinct symptom of activation.

We shall show later on that the exanthems of the acute exanthematous infections (scarlet fever, measles) only become possible because

⁴⁸ Petersen, W. F., and Milles, George. Relation of Menstruation to Permeability of Skin Capillaries and the Autonomic Tonus of Skin Vessels, *Arch Int Med* 38 730 (Dec.) 1926.

⁴⁹ Muller, E. F., and Petersen, W. F. *Munchen med Wchnschr* 74 531 1927.

the skin and the mucous membranes have a diminished resistance toward the circulating toxin Muller, Metz and Myers⁵⁰ demonstrated such a pathogenicity for one exanthematous disease due to a known toxin, namely, the arsenical dermatitis following arsphenamine

Even the occurrence of halitosis in severe infections is due to the lessening of cell activity in the mucous membrane of the mouth, with diminution of the bactericidal power The idea that the fetor is of stomachic origin is incorrect, for the growth of bacteria in the stomach is not increased during fever, though the bacterial flora may ascend to the higher levels of the gastro-intestinal tract, as has been demonstrated by Arnold and Brody⁵¹ As a matter of fact, the stomach contents, when removed, have no such fetid odor Soor paradentosis, caries and the pityriasis versicolor of the cachectic patient have a similar origin insofar as the loss of the resistance of the tissue makes possible the infections named The loss of hair and the impairment of the growth of the nails give further evidence of the peripheral vascular disturbances

Before we enter into a discussion of similar changes in the other organs, we must discuss for a moment those reactions which serve for the protection of tissue when toxic substances or a virus have entered the skin and the mucous membrane We characterize them as inflammatory Intensity of change, and this in relation to the protection of tissue means the effectiveness of change, also depends on vegetative orientation of the tissue as such Examples of such influences are well known With the onset of fever—let us say the sudden onset of an angina—the exudate of a gonorrheal infection ceases for a time The formation of pus in a sterile turpentine abscess during a fever starts after defervescence, all evidences that an autonomic influence is of paramount importance in local inflammatory processes

The work of Kauffmann⁵² and of Petersen⁵³ presents further examples Particularly, the work of Kauffmann with cantharides blister during the course of lobar pneumonia seems to us of particular significance, because Kauffmann carried out his experiments without considering the autonomic orientation in its influence on the metabolism and reactivity of the tissues During the course of the febrile stage of pneumonia he observed a decided impairment of reaction He said

The exudates are peculiarly poor in the cellular elements Among the cells present lympho-histiocytic elements are completely absent, as are also eosinophile cells, so that the exudate consists practically of neutrophile leukocytes But even

50 Muller E F, Metz, G P, and Myers, C N Arsenic Lesions of the Skin, Arch Dermat & Syph **15** 186 (Feb) 1927

51 Arnold L, and Brody, L Am J Hyg **6** 672, 1926

52 Kauffmann, F Krankheitsforschung **2** 372, 1926

53 Petersen, W F, and Willis, D A Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch Int Med **38** 663 (Nov) 1926

the immigrative cell elements so represented are increasingly diminished in the more severe disease processes. It is only with the crisis—when the inhibitory influences on the skin have disappeared, that inflammatory irritability and particularly the intensity of the cellular processes again increase.

In this work with the cantharides blister, Kauffmann therefore described the dependence of the inflammatory reaction on the vegetative orientation. Some years ago, Muller⁵⁴ pointed out that every collection of leukocytes was associated with a dilatation of vessels. Such dilatation is inhibited during a period of general reaction to infection. Herein, just as in the inhibition or diminution of the mobilization of tissue cells in the inflammatory exudate, we can recognize the negation of this phase of tissue protection of the skin at times when the center of metabolic activity of the body has been transposed to the internal organs.

Gastro-Intestinal Tract and Change of Temperature—The reversal of such vegetative orientation can also be established. Arnold¹ showed that when the blood vessels of the skin and the peripheral tissues are active, the bactericidal properties (that is the self-protection of the tissues) in the gastro-intestinal tract, particularly of the duodenum and the upper jejunum, are diminished. Man, as well as animals, exposed to heat and high humidity show, not only a coincident diminution in the secretion of the gastro-intestinal fluids, but a diminution in the normal response of the gastro-intestinal tract to food. If one examines dogs in superheated rooms, bacteria are found passing the stomach and duodenum practically in 100 per cent of the cases, whereas in the animals kept under normal conditions of temperature the bacteria are killed. If one feeds such overheated animals meat poisoned with enteritis toxin, the animals die, whereas animals kept at normal temperature or a cool temperature survive. If one measures the organic function of these animals in terms of stomach and bile secretion, following ingestion of poisoned meat, then one observes a marked and occasionally a total inhibition in the animals kept too warm and an enormous reaction in the control animals. In the human being, we also have observed this diminution with external heat as contrasted with normal temperature and a correspondingly increased reaction at the time of actual chill. The susceptibility to gastro-intestinal infection increases notably at times of increased external temperature. This is not only the case when infected food or pathogenic organisms pass in fully virulent form through the stomach to the gastro-intestinal tract. Even the normal gastro-intestinal parasitic flora is no longer indifferent under these conditions. Thus, Arnold⁵⁵ showed that with increasing

⁵⁴ Muller, E. F. *Munchen med Wchnschr* 69 1506, 1922

⁵⁵ Arnold, L. *Am J Hyg* 8 604, 1928

external temperature the flora changes its character, as well as its range. Characteristically, the lower gastro-intestinal flora invades the upper region of the gastro-intestinal tract. Similar conditions underly the manifestations of gastro-intestinal morbidity in populations at the beginning of the warmer periods of the year or in persons who go from cold to tropical climates. With the associated increased activity of the periphery of the body, the functional capacity of the abdominal organs is diminished.

This, too, is not necessarily dependent on the actual height of the external temperature, but rather on the reactivity of the skin and the lungs at the time, and on the autonomic impulses that under those conditions leave the periphery and influence the gastro-intestinal tract and the abdominal group of organs, in general. The decrease of resistance of the gastro-intestinal wall—in other words, the increase of susceptibility—in warm climates and in the hot summer is therefore most apparent in the unacclimated persons, that is, with sudden and unaccustomed changes, rather than in persons who gradually accustom themselves to higher temperatures. This point is of epidemiologic importance for a variety of gastro-intestinal infections, as well as for tropical diseases.

In the liver, too, the local immunity of the parenchyma is clearly dependent on the autonomic orientation of the tissues and is only effective when inhibitory impulses are not predominant.

The normal increase in activity of the liver in chill and fever has been previously described in some detail⁵⁶. Secretion of lymph and bile increases tremendously and with it vascularization, function and cell permeability. The marked increase of the permeability of the cells and tissues, in general, does not involve a necessary penetrability for all substances present in the blood. Despite continuous intravenous injection of living *B. coli* in the animal over experimental periods lasting for hours, the lymph of the thoracic duct remains free from bacteria. That is, the sterility of the lymph is constant as the function of the liver increases. On the other hand, bacteria are being constantly excreted into the bile passages. If such an experimental injection of *B. coli* is continued long enough (for ten, fifteen or twenty hours), one arrives at a time when the function of the liver is apparently rapidly diminished. At this time, the peripheral constriction of the vascular bed is also broken, and the animals show a peripheral hyperemia. In the liver, the vessels contract, the permeability of cell and tissue is diminished, as is the production of lymph and bile. At the time of this injury, red blood corpuscles appear in the lymph stream, proteolytic

⁵⁶ Petersen, W. F., Muller, E. F., and Boikan, W. J. Infect. Dis. **41** 405, 1927.

enzymes are markedly increased, the temperature falls, and some of the bacteria make their way into the lymph stream. Later this picture may be reversed.

Here, too, we see that the characteristic balance between the skin and the mucous membranes of the mouth, on the one hand, and the mucous membranes of the gastro-intestinal tract, on the other, may also influence the local resistance of tissue in other organs by means of a supererogated vegetative control.

These observations seem of certain importance in various directions, not only for the understanding of such processes as herpes, the infections of the mucous membranes of the mouth with parasitic invaders previously latent, and the catarrhal conditions of mucous membranes, in general, during infectious diseases and following chilling of the body surfaces, but for the understanding of gastro-intestinal manifestations in persons in unaccustomed warm climates, and of the status of the liver in the course of septic infections. From them we may be permitted to make certain deductions concerning the susceptibility of organs and tissues, in general.

The protection of normal tissues against an infection does not depend to any great degree on immune powers of the serum, but is, as every other function of the body, due to the cellular activity of the tissues and therefore is closely associated with the vegetative impulses and the vegetative status as particularly manifest in vascular alteration. One realizes, too, that the cellular tissue functions, on which local resistance depends, are controlled (as are all other functions of cells and tissues) in their responses and activity not only by the anatomic and functional activity of the individual elements as single cell organisms might be, but by certain limitations of their potential possibilities placed on them by more remote organic processes that directly influence the intensity of the vegetative orientation not only of the entire body, but of the local organs and tissues. It is possible, therefore, that with complete anatomic and physiologic integrity of the tissues, and despite the manifest danger due to the local infection, the local resistance of tissue may fail because it is inhibited through influences which, originating in remote regions, influence the local functional status. How this inhibition of functional response in the tissues may be brought about is clinically and practically unessential. At least two possibilities exist. Primarily, the diminution of function may be secondary to vascular dysfunction with an associated diminution of energy resources. Secondly, it may be directly imposed by the vegetative nervous impulses, or by chemical or hormone alterations acting on the blood vessels, as well as on the individual cells, either immediately or mediately.

The only fact that is of practical importance is that the local protection of the tissues, particularly those that have come in contact with

the surrounding world, is associated with and dependent on a superimposed vegetative orientation. Important is the knowledge that influences which may change the vitality of tissues, the functional capacity of the tissue and therefore the self-protective mechanism may remain objectively unnoticed, since they can be measured only in the end-result. In terms of relative resistance, they are perceptible only indirectly, that is, when functional inhibition has gone so far that the infection actually takes place.

It is not the mechanical integrity of the skin that offers the most effective protection, it is the vegetative condition of the tissue during which the adaptability of the cells can be developed to its maximum potential degree. It is seen that, on the basis of the splanchnoperipheral balance in the community of organ response, the more intense activity of the one group is balanced by a relative inhibition of the vital activity and capacity of another group, and that local resistance, as a measure of metabolic activity, as other functions, loses some of its potentiality under the influence of inhibitory forces. The local resistance of tissue is intimately bound up and dependent on local tissue elements and their functional capacity. With lowering of this functional capacity of the tissue, there occurs a lowering of the resistance of the tissue, irrespective of the origin of these inhibitory influences from without or from within, or of whether they are initiated by tangible organic changes or by psychic processes. The head cold, for instance, is not the result of a change of temperature to which one may have been exposed, but is the result of an individual difference in local resistance. Even in a severe draft with a considerable cooling, the temperature of the mouth, of the nasopharynx, of the musculature and of the joint cavities may remain approximately the same. With long continued intensive cold of the skin, of course, all the tissues and organs respond, the peripheral ones with a relative diminution of vascularity. We are therefore of the opinion (because of clinical observation) not only that articular rheumatism may be due to certain types of organisms, but that the joint membranes and the musculature have definite fluctuations of resistance against these invaders depending on the vegetative orientation of the moment. The Weber phenomenon is based on the fact that sudden displeasure or sadness leads to a diminution in the amount of blood in the periphery with a corresponding increase in the abdomen. But in psychic trauma, such as fright or fear or worry, a severe and long continued physical influence on the body can be brought about. In all of these one finds pallor of the skin, dryness of the mouth, loss of appetite, etc. One can readily see that the influences that make manifest many organic disturbances in association with psychic trauma do so because of the fundamental and underlying autonomic changes that we

have discussed in relation to the herpes virus. The organic changes depend, as this does, on the vegetative ability and adaptability of the local tissue.

EXOPHTHALMIC GOITER

Recently, Warthin,⁵⁷ in a discussion of exophthalmic goiter, reaffirmed his conviction that the underlying factor is constitutional, symptoms developing only as a result of abnormal reactions to stimuli which in a normal person would be met by physiologic adaptation. Oswald,⁵⁸ too, believed that the effect on the thyroid gland depends wholly on an instability of the nervous system in certain persons, an instability that Kessel, Lieb and Hyman⁵⁹ place in the myoneural junction. Warthin, furthermore, believed that "Graves' constitution" is associated with a "thymic-lymphatic" status and is characterized by hyperplastic primitive lymph nodes in the gland itself, which is involved in the disease only incidentally. Aschoff and Krehl both expressed similar views, and Miller⁶⁰ emphasized the probability of at least two active factors in the disease, one not identical with the substance that increases the basal metabolism.

There is a growing volume of clinical comment in agreement with this view.⁶¹ Bram⁶² tersely differentiated toxic adenoma by stating that here "the thyroid makes the body sick, in exophthalmic goiter (a constitutional disease) it is the body that makes the thyroid sick."

Our previous,⁶³ as well as present, series have made apparent a striking increase in capillary permeability in exophthalmic goiter, which, we believe, is basically associated with the clinical manifestations. Such an increase in permeability has been suspected as a result of the previous work of Eppinger and Hess. Gellhorn⁶⁴ has more recently proved the increase in permeability by direct experiments. Weil⁶⁵ drew the conclusion that the increase in permeability is to be correlated with, first, the increase in absorption and, second, the increased electrical conductivity of the tissues, and finally, with the increase in cell division.

57 Warthin, A. S. *Ann Int Med* **2** 553, 1928.

58 Oswald, A. *Klin Wchnschr* **4** 1053, 1925.

59 Kessel, L., Lieb, E. C., and Hyman, H. T. *A Study of Exophthalmic Goiter and the Involuntary Nervous System*, *J A M A* **79** 1213 (Oct 7) 1927.

60 Miller, J. L. *Proc Inst Med, Chicago* **7** 89, 1929.

61 Zondek, H., and Bansi, H. W. *Klin Wchnschr* **8** 1697, 1929.

62 Bram, I. *M J & Rec* **129** 579, 1929.

63 Petersen, W. F. *The Permeability of Skin Capillaries in Various Clinical Conditions*, *Arch Int Med* **39** 19 (Jan) 1927.

64 Gellhorn, E. *Das Permeabilitäts Problem*, Berlin, Julius Springer, 1929, p. 341.

65 Weil, R. *Klin Wchnschr* **8** 852, 1929.

observed in exophthalmic goiter. Weil found that thyroxin in small doses increases liver autolysis, which is due, presumably, to colloid chemical membrane changes with increased permeability. The clinical interest, as well as the physiologic interest, must therefore turn from the supposition that the effect is on the nerve endings as an intermediary. We are really dealing with a direct membrane change.

Dresel,⁶⁶ who also observed an increase in amino acids in liver autolysis following the injection of thyroxin, made use of the increased oxidation in the liver and testicle by injecting small doses of blood of the exophthalmic patient into a mouse.

The liver under these conditions becomes glycogen-free. From his experiments he concluded that the active agent circulating in the blood of the exophthalmic patient is far more active than any thyroxin preparation.

Mora⁶⁷ studied the shortening of the resorption time of intracutaneously injected salt solution in exophthalmic goiter, and Asher⁶⁸ made use of a similar dye test to demonstrate the central (sympathetic) effect on the thyroid gland.

The increase in permeability associated with increased metabolic activity should be followed by a negative calcium balance—and that it is, was recently demonstrated by Aub⁶⁹ and his associates, who also noted that osteoporosis may appear during the course of the disease.

Our observations indicate that the increased permeability determined by the blister is not necessarily related to the increased basal metabolic rate. In this respect, the results correspond with those noted in the markedly sympatheticotonic and nervous group in the members of which we observed an increased permeability without an increase in the basal rate. This fact, among others, inclines us to the view that we are dealing with two distinct factors—one, an underlying change in tissue reactivity, and another which is distinctly related to the calorogenic effect of the thyroid secretion. The question concerning the duality or multiplicity of the effect on the thyroid gland has repeatedly been raised, most recently by Csépai,⁷⁰ who, judging only by the effects on blood pressure, denies the probability.

The reactivity of the skin in patients with exophthalmic goiter presents a number of interesting features. The erythema after the applica-

66 Dresel, K. *Verhandl f inn Med u Kinderh*, Berlin, Jan 7, 1929, abstr., *Klin Wchnschr* 8 425, 1929.

67 Mora, J. M. *J M Sc* 177 153, 1929.

68 Asher, L., and Pfluger, O. *Ztschr f Biol* 87 115, 1927.

69 Aub, J. C., Bauer, W., Heath, C., and Ropes, M. *J Clin Investigation* 7 97, 1929.

70 Csépai, K., and Fernbach, J. *Arch f exper Path u Pharmakol* 129 256, 1928.

tion of ice appears rapidly, and the resistance of the skin to electric current is lowered, as Richter ⁷¹ has previously noted

Lueg and Grassheim ⁷² studied the capacity of the skin for polarization in thyroid disease and noted that the increase in the basal metabolic rate usually parallels the increase in capacity for polarization. Curiously enough, the upper and lower portions of the body may show considerable difference. Nothhaas ⁷³ in examining the dermographic reaction, found a longer latent period in exophthalmic goiter.

Hoke ⁷⁴ made use of a traumatic reaction (carbolic salt) and demonstrated an increased reaction of the skin in exophthalmic goiter and also after injections of thyroxin. Similar increases in reactivity were noted when milk or typhoid vaccine was injected.

In our preliminary discussion, we pointed out the occurrence of a dissociation of certain changes of the skin from the metabolic rate. We called attention to the fact that, following operation, the basal metabolic rate might return to normal but certain of the alterations of the skin become more pronounced. Such a dissociation of symptoms is, of course, a common observation in exophthalmic goiter and merely confirms our impression that the underlying change is dual. The treatment, too, would indicate this. Zondek ⁷⁵ grouped the methods under three heads: (1) operative removal of the thyroid gland, (2) fixation of thyroxin in the thyroid gland (with iodine) and (3) treatment with certain of the narcotic drugs that change the surface of the cell.

König ⁷⁶ added to this, thorough alkalinization, a procedure that might seem logical from the probable effect on the membrane of the cell.

THE NERVOUS PATIENT

It will be recalled that our nervous patients had a relatively low level of potassium with a practically normal level of calcium in the serum, were in general, then, usually showed an increased permeability of the capillaries, had a high resistance of the skin to electric current and a rather delayed reaction to ice.

Glaser ⁷⁷ reported that there were observable differences in the amount of calcium in the serum in different psychic states in the same person.

⁷¹ Richter, C. P. Electrical Skin Resistance. Diurnal and Daily Variations in Psychopathic and Normal Persons. *Arch. Neurol. & Psychiat.* **19**: 488 (March) 1929.

⁷² Lueg, W. and Grassheim, K. *Ztschr. f. klin. Med.* **110**: 531, 1929, *Klin. Wchnschr.* **7**: 647, 1928.

⁷³ Nothhaas, R. *Klin. Wchnschr.* **8**: 820, 1929.

⁷⁴ Hoke, E. *Wien. klin. Wchnschr.* **33**: 904, 1920.

⁷⁵ Zondek, H. *Verhandl. f. inn. Med. u. Kinderh.*, Berlin, Jan. 7, 1929, abstr., *Klin. Wchnschr.* **8**: 425, 1929.

⁷⁶ König, W. *Klin. Wchnschr.* **8**: 634, 1929.

⁷⁷ Glaser, F. *Med. Klin.* **20**: 1237, 1924.

Tomasson ⁷⁸ published the most extensive work, studying the mineral metabolism of a large series of psychopathic patients. From his studies he concluded that the calcium fluctuations precede periods of mental instability and that they are inversely proportional to the mood of the patient. In the maniacal periods of maniac depressive insanity, the calcium in the serum is increased and he did not find any low values. Movement in itself is not responsible for this, although under hypnosis there is some lowering of the level. Alterations of the mineral equilibrium of the serum which Tomasson described would be indicative of a loss of calcium from tissues with a coincident penetration by potassium. With it, he found a slight alkalosis.

Hoff and Werner's ⁷⁹ experiments indicate that in the neurotic patient one is dealing primarily with a lowering of the threshold between the vegetative and psychic centers, leading to obvious instabilities.

Kraus ⁸⁰ definitely grouped "neurasthenia" as a vegetative disturbance, i. e., vagolability, electrolytic alterations not only being associated with the vegetative-neurotic stimulation but determining the type of the reaction.

Regarding the vegetative status as the fundamental background of all reactions, reproductive, developmental—irritability, in general—he conceived the neuroses as distinctly constitutional (as, clinically, they obviously are) with general psychic manifestations, or as organ neuroses with local vagotonic or sympathetotonic overbalance. He assumed that it is potassium which plays the large rôle—nonionized potassium going over to ionized forms on stimulation, this would correspond with our observations. Insofar as the ultimate status of the individual (vital periodicity, reactivity) is, in its final analysis, the result of a balance between cosmic (external) and internal stimuli, we can understand that the constitutional status plus the conditioning effects influence the psychic reactions just as they would any other organ or tissue.

While there seems little doubt that we may legitimately associate changes in the permeability with functional changes in the nervous apparatus, the converse, that the nervous system may change the permeability of the capillaries is also probable, we may be dealing with a circular mechanism.

We have repeatedly stated that the stimulation of the sympathetic side of the autonomic nervous apparatus is associated with diminished

⁷⁸ Tomasson, Helgi. *Undersøgelser over nogle af blodets elektrolyter (Ca, K, Na, H) og det vegetative nervesystem særlig hos patienter med manodepressiv psykose*, Copenhagen, Levin & Munksgaard, 1927.

⁷⁹ Hoff, Hans, and Werner, Paul. *Klin. Wehnschr.* 7 346, 1928.

⁸⁰ Kraus, F. *Klin. Wehnschr.* 6 537, 1927.

capillary permeability Vessels that have been deprived of their sympathetic innervation are more permeable⁸¹

The work of Gellhorn⁶⁴ definitely proving the increased permeability following pilocarpine and diminution following epinephrine, is in line with related demonstrations by many observers We would, however, call attention to the fact that these effects are probably direct effects on the cell membranes With thyroid and sex hormones increasing permeability (the observations of Asher, Gellhorn, Frohlich and Zak⁸² and others are convincing) and epinephrine and pituitrin diminishing permeability, and with a regulatory effect of the nervous system in controlling the output of the glands of internal secretion made probable, we can understand that an overflow of nervous impulses to such glands in certain persons would change tissue permeability Asher and Pfluger⁸³ demonstrated increased activity of the thyroid gland under such conditions This would in turn increase capillary permeability in general

There is a close parallelism between "nervousness," capillary permeability, permeability of the meningeal barrier and the K/Ca ratio In the menstrual cycle, the nervous manifestations are clinically obvious The related blood chemistry has been well developed⁸⁴ Heilig and Hoff⁸⁵ demonstrated the increased permeability of the meninges, and we have shown an increase in capillary permeability⁴⁸ In our present series, the "nervous" persons have, in general, a distinct increase in permeability and with it as a group a low K/Ca ratio

We have had the impression for a number of years that mental instability can result from changes in the ionic equilibrium and from changes in the capillary permeability just as such alterations may change the reactivity of other tissues in the body In a woman with a puerperal psychosis, for instance, we observed an unusually high capillary permeability⁸⁶ In another instance, that of an individual in this series, we called attention to the fact that the patient's high capillary permeability occurred during a time of emotional stress incidental to stock market losses

Perhaps no more striking association of mental disturbances with alteration of the vegetative system (particularly muscular abnormality) exists than in catatonia Here we have definite evidence of the control

81 Yamamoto, J Biochem Ztschr **145** 201, 1924 Gabbe, E Ztschr f d ges exper Med **51** 728, 1926

82 Frohlich, A, and Zak, E Klin Wchnschr **8** 1540, 1929

83 Asher, L, and Pfluger, O Ztschr f Biol **87** 115, 1929

84 Riddle, O Proc Am Philos Soc **66** 497, 1927

85 Heilig, R, and Hoff, H Klin Wchnschr **3** 2049, 1924

86 Petersen, W F, and Lash, A F Alterations in Permeability of Skin Capillaries During Pregnancy and Puerperium, Arch Int Med **39** 12 (Jan) 1927, table 3

of the clinical picture through ionic alterations Reese,⁸⁷ together with Loevenhart and Lorenz, demonstrated complete (though transient) restoration of catatonic patients to a normal condition when the latter were stimulated by means of carbon dioxide respiration Gordonoff and Walther⁸⁸ also showed a marked increase in potassium in the blood and blood corpuscles of such patients

GLAUCOMA

Our examinations indicate that the patient with glaucoma has a lability of the cardiovascular renal system This seems in accord with the observations of other investigators Sulzer's⁸⁹ observations led him to believe that primary glaucoma is due to a vascular disturbance Schmidt⁹⁰ noted that the water balance of the body is atypical in glaucoma Thus, in the normal person, the ingestion of water is not followed by a change in eye pressure, in the glaucomatous patient, the pressure is increased While Schmidt does not believe that the effect is wholly osmotic, he does insist that it concerns a capillary change

One must, of course, not forget that local anatomic changes—size of the lens, dilatation of the pupil, etc—are probably the determining factors, the initiation of the disturbance may, however, be closely related to sudden changes in capillary permeability Goldenburg⁹¹ recently discussed this subject in some detail

TUBERCULOSIS

Constitution—The human body reacts fundamentally in two different ways to tuberculous infection one resulting in a relatively benign process, developing slowly, becoming quiescent through cicatrization and proliferative, the other resulting in an exudative process with fluid effusion, relatively rapid progression and dissolution of tissues Clinically, we meet every phase of resistance fluctuating between these two extremes, extremes which must depend on differences in irritability of the tissues The greater the irritability the more marked is the response, the greater the tendency to an exudative process The less the irritability the greater is the tendency to cicatrization

With these premises granted, the problem obviously involves the autonomic status of the organism as a whole, the status of the various organs and the question of variations in the vegetative status as modified by the infection

87 Personal communication to the authors

88 Gordonoff, T, and Walther, F *Klin Wchnschr* 8 1179, 1929

89 Sulzer, F *Munchen med Wchnschr* 75 768, 1928

90 Schmidt, K *Med Klin* 24 859, 1928

91 Goldenburg, M *Illinois M J* 52 474, 1927, *Am J Ophth* 11 290, 1928

It also must be kept in mind that even the acutely exudative process may result in utter destruction, i. e., digestion and removal of the virus and the inflammatory exudate. This latter method is probably a common method of disposal of the smaller lesions, much more common, than mere clinical observation would lead one to suspect.

Of course, the relation of "constitution" to tuberculosis is involved in this problem and is one that has interested physicians since time immemorial. The difficulty has been the definition of the term "constitution." In this way the "asthenic," "phthisical," "respiratory" type of the French has always been stamped as that of the potentially tuberculous person.

Borchardt⁹² discussed the reactivity of the tissues to tuberculous infection in relation to constitutional types. In the "Status-Irritabilis" of Wunderlich, he found more localization in the mucous membranes, the skin, the serous membranes, etc., with a relatively good prognosis and good connective tissue reactions. In the "asthenic" type (Stillei) or the lymphatic atrophic type (Pfaundlei) there is apparently a lessened reaction. We are dubious concerning the value of such classifications of constitution for the reason that in the adult the genotype must be greatly modified by the conditioning factors. One of the most important of these we consider to be the probability of a relatively long established preexisting tuberculous infection dating, not infrequently, from childhood. The tuberculous adult who is finally classified as of the "asthenic" or "phthisical" type must frequently be what he is—physically, physiologically and psychically—because of this infection.

While one ordinarily thinks of constitution in its more tangible form, one forgets the possible constitutional differences in the organ reactions and tissue reactions. Thus a congenital deficiency may indeed be expressed anatomically in the structure of the elastic tissue of an organ or in a certain degree of infantilism or in the more rapid senescence that one sees commonly in the teeth or the hair or the structures of the eye in certain families.

The Autonomic Status—Considerable literature has developed that deals with the autonomic nervous system and tuberculous infection. In this country, Pottenger⁹³ has for many years pioneered in studying symptomatology with particular relation to the underlying autonomic alteration. There is no uncertainty concerning this phase of the problem nor is there any question concerning the general autonomic instability as expressed in the reactions of the vasomotor, the gastro-intestinal and the mental apparatus. Redeker⁹⁴ has but recently reemphasized the

92 Borchardt. *Deutsche med. Wchnschr.* **47** 1159, 1921.

93 Pottenger, F. M. *Symptoms of Visceral Disease*, St. Louis, C. V. Mosby Company, 1929.

94 Redeker, F. *Beitr. z. Klin. Tuberk.* **70** 259, 1928.

general psychic instability as part of the reaction of the tissues to the invading organism. A most interesting histologic confirmation has come from Michejew and Pawljutschenke,⁹⁵ whose conclusions we shall quote at some length.

The patho-physiological explanation of the clinical findings in tuberculosis is often most conflicting, due we believe, to incomplete methods of examination. There is no doubt, however, that the tuberculous processes bring about changes in the functions of all organs, not only directly, but indirectly, through pathological alterations of the vegetative endocrine correlations. The entire "vegetative system" in the sense of Zondek-Kraus is destroyed.

Our examinations show that the tuberculous processes bring about diffuse changes in the vegetative centers. It is therefore impossible to associate definite vegetative findings with strictly limited anatomical lesions. We assume furthermore that in the central nervous system, no fixed centers for every type of metabolic activity exist, but that we deal rather with the projection of certain physico-chemical processes on certain nuclei. The diffuse character of the lesions found by us lead us to suspect that in tuberculosis, certain alterations exist that accelerate the penetration of the toxin into the central nervous system.

Leaving aside the factor of predisposition or constitution, we should like to point out that one of the chief factors must be this increase in permeability of the "hematoencephalic" or "capillary" barrier which makes possible this effect of toxin on the central nervous system. It is not necessary to dwell on the change in the concentration in calcium as one of the factors involved in this alteration.

The complexity of the balance between the individual vegetative system and the infection accounts for the multiplicity of symptoms and the variety of symptom complexes in tuberculosis.

It seems probable that the early change in the permeability of the "barrier" plays a role in the early appearance of certain nervous manifestations which we may regard as pre-tuberculous.

Changes in general cellular permeability apparently alter chronaxia, for Forster²¹ has shown that it is lowered by epinephrine, calcium chloride and parathyroid, and increased with hydrochloric acid, philocarpine, choline, thyroxin, etc., and Forster ascribed periodic fluctuations in sensitivity to impulses to alterations in chronaxia brought about by general changes in the permeability. Lapique and his co-workers⁹⁶ had previously demonstrated this phenomenon. Both peripheral and cerebral changes in permeability apparently directly influence the nervous response, and the dependence of the effect of the impulses on the state of the organ has been discussed previously at length.

With the recognition that the local autonomic status of the tissues is of importance in the resistance to tuberculosis, the study of that status has concerned a number of workers.

⁹⁵ Michejew, W. W., and Pawljutschenke, E. M. *Arch. f. Psychiat.* **84** 227, 1928.

⁹⁶ Lapique, M. *Soc. de biol. Paris* **74** 32, 1913. Obre', A. *ibid.* **88** 585 1923. Florkin, M. *ibid.* **97** 1804, 1927.

Eppinger and Hess⁹⁷ were the first to point out that the majority of tuberculous patients give a "vagotonic" reaction to epinephrine. Deutsch and Hoffman⁹⁸ reported that the patient with early tuberculosis gives a "sympatheticotonic" reaction to epinephrine. Later, the reaction is more irregular, with "vagotonia" preponderating. Dresel⁹⁹ confirmed this observation.

A most extensive series of observations was reported by Guth,¹⁰⁰ whose interpretation, in general, follows the line of Danielopolu. He noted that tuberculotoxin acts amphotropically, first irritating both components, later leading to a depression, with emphasis on the vagus side. In general, most of the exudative patients were found to be "vagotonic", most of the productive types, "sympatheticotonic".

Glaser's study,⁷⁷ as well as Kading's¹⁰¹ work, indicates that the chronic tuberculous person is "sympatheticotonic". Pende¹⁰ came to the conclusion that if the tuberculous person is first "sympatheticotonic" and then becomes "vagotonic," the prognosis is poor, whereas if the tuberculous person is primarily "vagotonic," the process is usually relatively benign. Géza,¹⁰² on the other hand, found "vagotonia" occasionally present with some productive forms.

Kamsler¹⁰³ studied the vascular response to epinephrine, atropine and neucisol in a group of tuberculous patients. He was careful to make the tests only in men and at the same time of the day. He found no apparent relationship between the vegetative response and the prognosis, but noted that the pyknic types responded with low blood pressure curves.

Interesting is his agreement that the vegetative response to these various pharmacologic agents is merely one of an accentuation of a pre-existing orientation and that it is dependent particularly on calcium concentration. He insisted that one should speak merely of an irritability or a depression of the vegetative system, as did Bovet.¹⁰⁴

The autonomic status as judged on the basis of the blood pressure response to epinephrine in our series indicates a decided lessening of the reactivity of the tuberculous group as contrasted with the group of 100 normal persons. So, too, of the twenty-four patients who died, those who lived the longest had the more marked "sympatheticotonic".

97 Eppinger, H, and Hess, L. *Die Vagotomie*, Berlin, 1910.

98 Deutsch, F and Hoffman, O. *Wien klin Wchnschr* **26** 569, 1910.

99 Dresel, K. *Ztschr f klin Med* **101** 70, 1924.

100 Guth, E. *Beitr z Klin d Tuberk* **53** 94, 1922, **54** 186, 1923, **55** 33, 1923, **60** 39, 1924. Glaser, W. *Ibid* **55** 390, 1923.

101 Kading, K. *Munchen med Wchnschr* **71** 225, 1924.

102 Geza, Gali. *Gyogyaszat* **62** 232, 1922, abstr. *Zentralbl f d ges Tuberc Forschung* **19** 31, 1923, **22** 493, 1924.

103 Kamsler, A. *Klin Wchnschr* **7** 110, 1928.

104 Bovet, A. *Schweiz med Wchnschr* **58** 483, 1928.

reactions to tuberculin when they were examined, and of the four patients who were losing weight at the time of examination but subsequently improved, three showed a "sympatheticotonic" reaction

We have repeatedly expressed our reservation concerning the use of the terms "sympatheticotonic" and "vagotonic" We should much prefer to discard them entirely, resolving the term into the various components, *i e*, the local status of the tissues, whether active or resting, whether with increased or diminished permeability, whether with dilatation or constriction of the vessels, whether with relative alkalosis or relative acidosis, etc The terms "sympatheticotonic" and "vagotonic" are altogether too conflicting and too broad to be useful

We shall examine the local reaction from this point of view About a tuberculous focus there exists a zone of tissue stimulation (irritation) which may range from slight and transient effects that are promptly reversed by the more remote cells of the focus, through all the stages of fatigue and finally to death In the stage of stimulation, the metabolic rate, acidity, permeability, cellular exchange and enzymatic (digestive) processes, are all increased, calcium leaves the tissue and sodium and potassium enter A general lessening of tissue cohesion takes place In general terms, we can regard this as an abnormal status of the vegetative balance in which the autonomic nervous system, the ionic equilibrium, the hormones and the tissue metabolites play their rôles

Tissue changes associated with autonomic derangement are usually associated with local injury, more rarely with changes in the entire organ and sometimes with alterations in the vegetative balance involving the entire body

1 Alterations in the nervous component of the vegetative system may originate from (*a*) purely psychic effects, (*b*) direct injury of nerves, as for instance, the pressure of enlarged mediastinal glands on the vagus, and (*c*) central (midbrain) injury, illustrated strikingly in some cases of postencephalitic parkinsonism and in some of the intoxications that follow bacterial or other poisoning

2 Endocrine dysfunction plays a rôle Diminution of the suprarenal secretion and perhaps of the pancreatic hormone would have a tendency to increase permeability, as would hyperfunction of the sex glands and of the thyroid gland The activity is, however, conditioned to a large extent by the ion equilibrium existing at the cell surface, *i e*, by the preexisting state of activity of the cell

3 Tissue reaction is also involved Increased acidity increases permeability, and this goes hand in hand with a release of calcium from the cells

The Vascular Reaction to Tuberculin—Given this background, let us examine the status of the tuberculous tissue and the tuberculous

person as a whole. We know, in general, that the reaction of the tuberculous tissue, as recently shown by Schade and Claussen,¹⁰⁵ is on the acid side (from p_H 7 to p_H 7.3) and exactly at the optimum for growth of the tubercle bacillus. We know, too, that the peripheral dilatation of blood vessels depends not on central vasomotor regulation, but on the peripheral effects of dissimulation, including primarily, increased acidity, as well as the effects of histamine and acetylcholin.

Fleisch recently added a demonstration which is most convincing¹⁰⁶

Tuberculin itself always causes vessels to dilate.

In preceding discussions, we have pointed out that stimulation of smooth muscle (in the metabolic and membrane sense) is associated with relaxation, i. e., lengthening of the cell. The reason for this seemingly paradoxical point of view we need not again elucidate, the physiologic observations have been generally accepted. When we extend this to the smooth muscle of the blood vessel wall, direct stimulation of cells must result in the dilatation of the vessel. Epinephrine, which makes the membrane less permeable, apparently causes contraction, irrespective of its presumable effect via the sympathetic mechanism.

Tuberculin stimulates the normal organism,¹⁰⁷ in the tuberculous animal, the stimulation may proceed to fatigue. We should expect that in the isolated vessel preparation perfused with tuberculin would cause dilatation. Experiments of Preobraschewsky¹⁰⁸ are now available on this point. He found that tuberculin causes the normal vessels to dilate, with contraction following. In the tuberculous animal, the preliminary dilatation persists indefinitely. Bullion acts like tuberculin.

He also observed that a vessel preparation of animals with advanced tuberculosis showed a lessened reactivity to epinephrine. We believe this to be explained on the basis of the well known observation that epinephrine causes little or no contraction of vessels in irritated (inflammatory) regions. When tuberculin was injected into animals and vessel preparations were then perfused, the reaction to tuberculin (and bullion) was irregular. Similar experiments were made by Friedberger and Seidenberg.¹⁰⁹

Here a physiologic preparation offers the counterpart of the intravital phenomena that take place when tuberculin is injected or that must obtain when tuberculin is released from a focus. The vessels are

105 Schade, H., and Claussen, F. *Beitr. z. Klin. d. Tuberk.* **62** 300, 1925.

106 Fleisch, A. *Klin. Wchnschr.* **8** 1315, 1929.

107 Levinson, S. A., and Petersen, W. F. *Am. Rev. Tuberc.* **15** 681, 1927.

108 Preobraschewsky, A. M. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **63** 132 and 139, 1929.

109 Friedberger, E., and Seidenberg. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51** 276, 1927.

directly stimulated. In place of a normal reversal occurring, the tissue is readily fatigued and reversal is delayed, i. e., dilatation persists.

Therapeutic agents that have been useful in tuberculosis are those most frequently directly active on the capillaries, and even that most specific agent, tuberculin, is effective in the therapy of tuberculosis probably not because of its immunologic properties but because of its influence on the caliber of the arterioles and the permeability of the capillaries (and tuberculous lesions), as originally supposed by Moro.

It is the vascular reaction that must always be regarded as the basis of any understanding of the tuberculous lesion. Physiologic vascular processes, which can be interpreted on the basis of stimulation, of rest or of fatigue, have been disguised by obtuse and conflicting immunologic concepts. We have come to consider resistance without reference to specific concepts, and Kalbfleisch¹¹⁰ seems to have reached the same position when he stated that there is no room for the term "immunity" in the pathology of tuberculosis. This is quite apart from the persistent attack on the specificity of the tuberculin reaction¹¹¹. We have felt justified in concluding from our experiments¹¹² that the reaction of the normal animal differs from that of the tuberculous animal only in degree. Kalbfleisch's conclusions in this connection are as follows:

There is only one thing that differentiates the effect of tubercle bacilli in tuberculous animals from the effect in the healthy animal, these are differences in the reaction of the vascular system, which, depending on susceptibility to the irritation and reactivity of the nervous elements of the vascular bed of the tuberculous animal, bring about quantitative differences from the reaction of the normal animal, and thereby bring about quantitatively altered effects in the cells and fibers of the tissue.

All the therapeutic agents of the "reactive" class, tuberculin, sodium aurothiosulphate, hetol, etc., act seemingly in a relatively simple way¹¹³. They first make the tissues more permeable, and later the tissues become less permeable for a considerable period of time.

The focal reaction, whether in the form that is obvious clinically or consisting merely of the imperceptible biologic actions following the injections of minute doses of the agents in question, is a reaction that depends on changes in permeability of the capillaries about the tuberculous focus.

110 Kalbfleisch, H. H. *Beitr. z. Klin. Tuberk.* 70 465, 1928.

111 Selter, H., and Bloomenberg, W. *Beitr. z. Klin. d. Tuberk.* 66 105, 1927.
Beiling, R., and Keller, W. *ibid.* 69 577, 1928. Keller, W., and Dolter. *ibid.* 60 444, 1928.

112 Petersen, W. F., Jaffe, R. H., Levinson, S. A., and Hughes, T. P. *J. Immunol.* 8 387, 1923. Petersen, W. F., and Levinson, S. A. *Am. Rev. Tuberc.* 8 122, 1923.

113 Levinson, S. A., Petersen, W. F., and Milles, G. *Am. Rev. Tuberc.* 16 285, 1927.

Biologic processes, such as the menstrual cycle the effects of season, etc., that are associated with an increase in capillary permeability and autonomic imbalance are apt to be associated with clinical activation

A most enlightening condition concerns the relation of the mortality from tuberculosis to the season. The association of clinical activity with the spring goes back to Hippocrates. A recent statistical correlation is that of Herrup from the Faroe Islands¹¹⁴. The change in the K/Ca ratio and the seasonal changes in the size and activity of the organs made apparent in the work of Riddle¹¹⁵ and Brown⁹ bring us nearer a logical explanation of the clinical observations.

Clinically advancing tuberculosis is associated with increased capillary permeability, healed tuberculosis with diminished permeability. It might seem warranted to draw the conclusion that increase in capillary permeability however produced would unfavorably influence a tuberculous lesion, and that conversely diminished permeability must be associated with improvement.

We shall not endeavor to include in this summary a review of all the results of the examinations made but shall discuss briefly only the more important phases of the work.

Correlations Based on Clinical Classifications, Weight Curve, Clinical Prognosis and Fatalities—The Clinical Classifications of the National Tuberculosis Association (table 2, part VII A). Apart from the obvious correlations (tuberculosis fixation Daranyi reaction, basal metabolic rate, pulse rate, etc.), there are no consistent changes as we proceed from the incipient A to the far advanced C cases. We might anticipate this. The incipient A group will include patients in whom the disease may develop rapidly, may heal or may become chronic. The far advanced C group will include patients who have had chronic tuberculosis for years, with relatively high resistance. In addition, there will be many persons with febrile tuberculosis, with peripheral vasoconstriction, made evident in the prolongation of the blister time.

Weight Curve (table 3 part VII A). The grouping of patients by relative increase or decrease of weight at the time of examination begins to offer something more tangible. It is to be noted that the persons with healed tuberculosis (roentgen shadows only) have a permeability of 65. Persons with roentgen evidence of active tuberculosis (very chronic) have a permeability of 59. Our sanitarium group shows a progressive increase to 69.6. There is, however, no consistent relation to the blood chemistry but the blood proteins increase, and the McClure-Aldrich test is markedly shortened.

114 Herrup. Beitr. z. Klin. d. Tuberk. 68 739, 1928.

115 Riddle, O. Am. Naturalist 61 481, 1929.

Prognosis (table 9, part VII A) Here we begin to obtain interesting clinical and laboratory correlations. The relation to permeability and to calcium has been discussed. We note that the "vagotonic" reaction to epinephrine increases, the epinephrine flare becomes smaller while the thyroxin flare becomes larger, the cholesterol/lecithin ratio becomes smaller, the McClure-Aldrich test becomes shorter and the tuberculin reaction smaller.

Fatalities (table 10, part VII A) When, finally, we consider the patients who died and place them in two groups, (those that lived an average of forty-five months after the onset of clinical activity and those that lived an average of sixty-five months), we find that the less resistant group had a high capillary permeability, much less calcium, less cholesterol, a higher globulin content and a shorter McClure-Aldrich time, while there were more "sympatheticotonic" persons in the group that lived longest.

Calcium—We must regard the calcium metabolism as in some way closely associated with the clinical condition of the patient. In the group with low calcium, for instance, we find more deaths. We find that the persons with healed tuberculosis have higher calcium (10.3), that persons with good prognosis have higher calcium (10.7 and 10.6), that those with stationary disease have lower calcium (9.1), as we then turn to those with poor prognosis, the calcium level again rises (10.2), owing, we believe, to the probability that with a negative balance, calcium is being mobilized from the tissues. We have previously discussed some of the literature dealing with calcium in tuberculosis (part III).

More and more clinical evidence is accumulating which indicates the importance of calcium in tuberculosis in regard to both the reactivity of the tissue and its influence on the disease process. Sternberg¹¹⁶ found lower serum calcium in the most advanced cases, Schaefer,¹¹⁷ an increase in the calcium in the lung in chronic tuberculosis. Sweany¹¹⁸ and his associates found the calcium levels about normal, and Hoyle,¹¹⁹ admitting the clinical impression of improvement with calcium, regarded the experimental evidence as still lacking. He found an early increase in calcium in rabbits infected with tuberculosis, with a terminal decline. The lack of experimental confirmation is, however, not necessarily a criterion of clinical value, for the reason that tuberculosis in the guinea-pig and in the rabbit, particularly, is decidedly different from tuberculosis in man. As a matter of fact, Henner¹²⁰ observed that when

116 Sternberg, T. Beitr. z. Klin. d. Tuberk. **71** 737, 1927

117 Schaefer, R. Beitr. z. Klin. d. Tuberk. **69** 86, 1928

118 Sweany, H. S., Wethers, A. T., and McCluskey, K. L. Am. Rev. Tuberc. **8** 405, 1924

119 Hoyle, J. C. Quart. J. Med. **22** 451, 1929, J. Pharmacol. & Exper. Therap. **34** 317, 1928

120 Henner. Beitr. z. Klin. d. Tuberk. **51** 56, 1929

calcium dust ($\text{Ca}[\text{OH}_2]$) was used, tuberculous animals not only showed less involvement than animals exposed to other dust, but actually less than the control animals not exposed to dust. The clinical literature, as mentioned previously, is rather conflicting, and various methods have been suggested for the administration of calcium, as well as various indications. Thus Siegel¹²¹ stated that he obtained improvement in 50 per cent of his cases with calcium inhalation. Becker¹²² treated 150 patients with intravenous medications and mentioned improvements, particularly in bilateral involvements.

Cholesterol—That cholesterol usually diminishes with progressive tuberculosis has been frequently noted. This, of course, is in line with the change in cholesterol metabolism apparent in other infections.¹²³ In recent work, Shope¹²⁴ brought experimental evidence that increasing serum cholesterol probably plays some rôle in prolonging the life of experimentally infected guinea-pigs, confirming clinical observations that date back a number of years.¹²⁵ Borchardt,¹²⁶ as well as Leupold and Bogendorfer, recently presented further experimental evidence concerning the usefulness of cholesterol in increasing resistance to infection, an increase which seems to follow specific immunization, too.¹²⁷ The association of a low cholesterol in tuberculosis with poor prognosis was noted by Rieter,¹²⁸ and is in line with the results of our observations.

It is rather interesting to note that Glaser¹²⁹ published clinical observations indicating that the cholesterol level of the blood may change with changes in the psychic state just as does the calcium level, while Wade¹³⁰ found an increase in cholesterol associated with a decrease in the serum calcium.

Reactivity of the Skin—The reactivity of the skin of the tuberculous patient has been a subject of study for so many years by so many investigators that we shall make no effort to review the literature, but merely point out that there is a general recognition of the fact that, apart from the so-called "specific" factor, the degree of reactivity is dependent on the status of the skin, i. e., that the systemic factors play a decided rôle. Thus, the reactivity to tuberculin diminishes in the

121 Siegel, H. *Ztschr f Tuberc* **53** 256, 1929

122 Becker, A. *Ztschr f Tuberc* **53** 198, 1929

123 Heening, B. H. *J Biol Chem* **53** 167, 1922. Gabriela, J., and Vior, V. *Arch d mal de l'app digestif* **18** 601, 1928. Heinze, V. *Ztschr f Tuberc* **52** 199, 1928

124 Shope, R. *J Exper Med* **48** 321, 1928

125 Valois, G. *De la cholestérinémie au cours de la tuberculose pulmonaire*, Lyon and Paris, A. Maloine et fils, 1912. Farini, A. *Gazz d osp* **35** 993, 1914

126 Borchardt, W. *Klin Wchnschr* **8** 1179, 1929

127 Barbara, M. *Arch di pat e clin med* **8** 379, 1929

128 Rieter, H. *Klin Wchnschr* **8** 1158, 1929

129 Glaser. *Klin Wchnschr* **6** 2377, 1927

130 Wade, P. A. *Am J M Sc* **177** 790, 1929

terminal stages in tuberculosis, during intercurrent disease and with "desensitization" due either to tuberculin therapy or as a result of non-specific injections

Nor is it possible to review the extensive literature concerning reactivity of the skin, in general. The monographs of Lewis,¹³¹ the shorter works of Hecht,¹³² Pulay¹³³ and Luthlen,¹³⁴ the reviews of von Groer⁴⁶ and Ebbecke¹³⁵ are available for this purpose.

We would, however, refer again to the work of Kauffmann.⁵² Kauffmann observed that when he placed cantharides on the skin of a patient with pneumonia, several distinct stages of reactivity could be distinguished. First, during the febrile period, he observed a delayed or absent reaction. Second, with defervescence a marked reaction, third, after defervescence, a period of transition during the next ten days to a maximum monocytic reaction in the exudate, fourth, for a varying interval, another period of inhibition or delayed reactivity (adaphorea of von Groer, presumably not the same as local immunity in the specific sense).

As cantharides constitute a chemical irritant acting primarily on the cell membranes, specific sensitization plays no rôle, but the results are nevertheless of interest for the tuberculin reaction. Let us examine the possible correlation.

1 During the febrile stage there exists a peripheral inhibition (vasoconstriction). Cantharides can act on the cells, but little or no exudate forms. The direct injury to the cells is great because there is no dilution, and healing takes place slowly (see discussion of herpes). Applied to tuberculosis and the tuberculin reaction, it means that during the febrile stage of an intercurrent disease, the tuberculin reaction is inhibited because of the change in the status of the skin, during the terminal stages of tuberculosis itself, this factor is also operative.

2 During the period corresponding to defervescence in pneumonia when, as Meyer pointed out, vascular dilatation is accentuated, this peripheral factor is negated, and vigorous reaction takes place. Applied to the tuberculin reaction, this corresponds to the period of maximum response when sensitization (i. e., direct cellular response and vasodilatation due to the direct effect of the tuberculin) prevails at a time during which peripheral vasodilatation is compensating for the increased metabolism going on in the body (i. e., during the period of vasomotor

131 Lewis, T. *The Blood Vessels of the Human Skin*, London, Shaw & Sons, 1927.

132 Hecht, A. F. *Ztschr. f. d. Ges. exper. Med.* **33** 23, 1923.

133 Pulay, E. *Stoffwechsel und Haut*, Vienna, Urban & Swartzenberg, 1923.

134 Luthlen. *Pharmakologie der Haut*, Berlin, Julius Springer, 1921.

135 Ebbecke, U. *Deutsche med. Wchnschr.* **50** 1, 1924, *Naturwissenschaften*

instability, when the tuberculotoxin has not yet stimulated the liver to the degree that the splancho-peripheral balance has become fixed. The autonomic skin function is, in other words, practically normal insofar as lability is concerned.

3 Finally, in the pneumonia patient, at varying intervals after the crisis (from three to five weeks), a period supervenes during which the skin is again nonreactive. Here we are not dealing with a peripheral vasoconstriction present during the acute febrile stage. The tissue cells have changed. The cell membranes are no longer irritated to the same degree by the same amount of the irritant. The cell membranes have become less permeable. Applied to tuberculosis we find the same picture during periods of relative quiescence of the lesions, with recovery, after a course of tuberculin treatment, or after a series of relatively bland nonspecific injections.

These are wholly nonspecific effects which influence the reactivity of the skin in general, but they are of importance for the problem of tuberculosis because the vegetative status of the skin and the vasomotor activity are underlying factors that determine the type of reaction to all toxic agents.¹³⁶

That these different states of reactivity of the skin are associated with differences in the underlying physicochemical equilibrium we need not again emphasize. However, the experiments of Klauder and Brown,¹³⁷ which are pertinent, must be mentioned. In their experiments, a correlation of the blood and skin chemistry with the intensity of the skin reaction is made evident.

Apparently, differences exist that depend on the type of irritant, for instance, calcium seems to be much more closely related to the effect of epinephrine and to the blister time, potassium, to the effect on the skin of thyroxin and caffeine. Needless to say, there are many other modifying factors (table 1, part I).

Leukocytic Reaction—Among the reactions that we have followed with particular interest has been the effect of the intracutaneous injection of a bland protein on the leukocytic curve.

¹³⁶ Roeckemann. Beitr. z. Klin. d. Tuberk. **49** 301, 1922. Stutz. Schweiz. med. Wchnschr. **54** 676, 1924. Schubert, A. Beitr. z. Klin. d. Tuberk. **69** 273, 1928.

¹³⁷ Klauder, J. V., and Brown, H. Experimental Studies in Eczema. I. A Study of the Sensitivity of the Skin of Rabbits to Chemical Irritants Under Experimentally Induced Conditions, Arch. Dermat. & Syph. **11** 283 (March) 1925, II. A Correlation of the Chemistry with the Irritability of the Skin of Animals Under Normal and Under Experimentally Induced Conditions, *ibid.* **15** 1 (Jan.) 1927, III. The Role of Sympathetic Nervous Irritability in the Rabbit, *ibid.* **19** 52 (Jan.) 1929, IV. The Correlation of the Potassium-Calcium Ratio in the Serum and in the Skin of Rabbits with the Irritability of the Skin, *ibid.* **20** 326 (Sept.) 1929.

Intracutaneous injections bring about systemic effects, not only through the agency of the injected solution, but through the stimulation of the skin. Perhaps this stimulation of the skin is associated with liberation of histamine, perhaps it is due to a purely autonomic upset of the type that we have illustrated in charts 2, 3 and 4. Lewis reported experiments in which multiple areas of irritation of the skin resulted in a distinct systemic effect due, according to his hypothesis, to the actual liberation of enough histamine to bring about a general reaction.

Our composite curves indicate that when patients are classified on the basis of increasing, stationary or decreasing weight, the leukocytic reaction in the losing group is that of a rather marked primary leukopenia following the intracutaneous injection. Such a group of patients shows a coincident lowering of the blood pressure. We ascribe this to the fact that in this group the splanchnic vascular bed is more easily thrown out of balance with consequent accentuation of splanchnic stimulation and dilatation and a resulting accumulation of leukocytes in the splanchnic area. The reactions merely afford additional evidence for the supposition of an altered vegetative status with progression of the disease.

Therapeutic Considerations—Granted that the tuberculous lesion can be made clinically innocuous in one of two ways—(1) by digestion and (2) by complete encapsulation—the former method would be supported therapeutically by any measures that increase vascularization, increase enzymatic processes, increase permeability or, in general terms, bring about tissue stimulation, with relative acidosis, or the so-called “parasympathetic status”¹³⁸. The inherent danger lies (1) in the possibility of dissemination of the virus, (2) in the diffusion of toxic products and (3) in the possibility that stimulation may proceed to fatigue and death. We can readily understand that only sluggish lesions of the peripheral type or small lesions in the more vascular organs can be so treated with any degree of safety.

The second method, complete encapsulation, would be supported therapeutically by methods that decrease vascularization, decrease enzymatic processes, decrease capillary permeability or, in general terms, bring about rest of tissue or a “sympathetic” status,¹³⁹ with relative alkalosis. Here one must assume a therapeutic indication in the more extensive lesions, especially of the vascular organs.¹⁴⁰

From the point of view of constitutional types, we can see that our heavy type should offer a general biologic status of diminished permea-

138 To be differentiated from vagotonia (see page 18)

139 To be differentiated from sympatheticonia (see page 18)

140 The vascular endothelium of the viscera—liver, kidney, spleen, gastrointestinal tract—is normally more permeable than that of the peripheral tissues

bility, lower metabolic rate and more sluggish inflammatory reactions that would seem favorable for the development of a slowly progressive, relatively benignant lesion. Presumably, in endocrine balances we would see less effect of the thyroid gland, with probably more effect of the pituitary gland, and in some cases more secretion of epinephrine.

Our slender type should offer two possibilities: a person, who, because of intense reactivity—with relative acidosis, increased metabolic rate, increased permeability, etc.—might, under certain circumstances, succumb to the infection rapidly, especially if infected with a large dose of the virus, and another person of the same type who might readily and rapidly dispose of tubercles, with relative freedom from clinical symptoms. The latter would presumably have more thyroid secretion, more sex gland secretion and varying degrees of suprarenal and pituitary activity.

It is perfectly obvious to us that in the intricate biologic picture of inflammation presented by tuberculosis innumerable possibilities exist. We have merely delineated the extremes. We would, however, reiterate that in clinical tuberculosis, it is the vascular mechanism that must always be in the foreground of consideration.

The particular therapeutic studies that have been introduced in the final paper of the tuberculosis series (VII C) are to serve only to illustrate several points in connection with the theoretical deductions; they are not to be regarded as clinical evidence for another cure for tuberculosis. They indicate that

- 1 Pilocarpine (case of sister A, part VII C), which makes the capillaries more permeable, may be followed by dissemination.

- 2 Epinephrine (case of sister B) which normally is not only diphasic but amphotropic, may, when it makes capillaries less permeable, diminish clinical activity, or may make the capillaries more permeable and increase clinical activity (case 2, under "Reports of Other Cases," part VII C).

- 3 Pituitrin, which apparently acts more specifically on the cell membrane in lessening permeability (even in irritated tissues) may lessen clinical activity (cases 4 and 5).

- 4 Alkalosis is apparently useful (case 1) and stimulation of the skin by means of a skin burn, which theoretically should result in a peripheral dilatation and a splanchnic constriction, may also be useful (case 3).

With investigators in tuberculosis becoming more and more interested in tissue activity as a factor in resistance, many therapeutic procedures will be offered and exploited. The Gerson diet has already been capitalized. Here a diet predominantly of vegetables and fruits with its tendency toward alkalinization is advised with a salt-free oat-

meal diet, with its contrary tendency, and a proprietary salt mixture is added for good measure. Of course, the clinical reports are conflicting. If the Gerson diet really tends to bring about tissue acidosis, it should be useful in the sluggish peripheral types of infection, and actually the results in infection of the skin seem to be encouraging. On the other hand, there appears to be little consistent effect in the pulmonary lesions. As is the case with so many cure-alls the proponents here forget the innumerable individual features of each clinical picture and that a therapy which may be admirable for a sluggish tuberculosis of the skin is by no means necessarily useful for a visceral tuberculosis.

Practically every "cure" has met with this fate, and it must be the fate of every type of treatment that depends on tissue reactivity for its curative properties. "Stimulating" substances—tuberculin, helio and sodium aurothiosulphate, for example—are active in sufficiently large doses by increasing permeability. And with large doses, injury almost invariably results. In small doses, they are sometimes useful because the transient stimulation and increased permeability are followed by a reversal—with a persisting impermeability. The agents that might presumably act in a contrary direction, epinephrine as originally suggested by Sargent, or calcium, may be useful when the preexisting state of the tissue is favorable. If not, one may get "paradoxical" effects with increased permeability and clinical injury. Even the physical agents, particularly heliotherapy, are followed by identical results. Sunlight may activate lesions in certain persons and may be useful in others.

We have the conviction that if we once begin to plan the therapeutic attack in tuberculosis less from the point of view of the immunologists and pharmacologists and more from that of the inflammatory reaction and its physiologic and physiochemical aspects, we shall be able to devise a more rational therapy.

What has been detailed for a chronic infection like tuberculosis has been presented merely to illustrate a point of view which we believe may be useful in other therapeutic problems.

THE EFFECT OF EXPERIMENTAL HYPERTHYROIDISM AND OF INANITION ON THE HEART, LIVER AND KIDNEYS^{*}

J P SIMONDS, M D
AND
W W BRANDES, M D
CHICAGO

The literature on the effects of inanition was reviewed by Morgulis¹ in 1923 and by Jackson² in 1925. As our paper was being prepared, Jackson's more recent review of the subject appeared.³ The effect of starvation on the body as a whole and on individual organs is fairly well established, in spite of certain contradictory reports. The feeding of thyroid has been shown to cause loss of body weight by Magnus-Levy,⁴ Farranti,⁵ Hewitt,⁶ Kuriyama⁷ and others. But, as pointed out by Kunde,⁸ the effect of thyroid feeding on the body weight of dogs varies within wide limits. In our series of dogs, three animals were of approximately the same initial body weight, namely, from 11.6 to 11.9 Kg. Each received 10 Gm of desiccated thyroid daily and all were kept on the same diet. One lost only 14.3 per cent of its body weight after forty-eight days of thyroid feeding, another 24.2 per cent after fifty-seven days, and the third 33.5 per cent after only thirty-two days (table 5 may be seen here).

Studies have been made of the weights of different organs in experimental hyperthyroidism but apparently only in rats, mice and rabbits.

* Submitted for publication, Oct. 4, 1929.

^{*} Read before the Chicago Pathological Society, Nov. 11, 1929.

^{*} From the Department of Pathology of Northwestern University Medical School.

^{*} Aided by a grant from the Fenger Memorial Fund.

1 Morgulis S. Hunger und Unterernährung. Berlin, Julius Springer, 1923.

2 Jackson, C. M. The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Company, 1925.

3 Jackson, C. M. Recent Work on the Effects of Inanition and of Malnutrition on Growth and Structure. Arch. Path. 7: 1042 (June) 1929.

4 Magnus-Levy, A. Berl. klin. Wchnschr. 32: 650, 1895.

5 Farranti, R. Brit. M. J. 11: 1363, 1913.

6 Hewitt, J. A. Quart. J. Exper. Physiol. 8: 113, 1915.

7 Kuriyama S. Am. J. Physiol. 43: 481, 1917.

8 Kunde, Margaret M. Am. J. Physiol. 82: 195, 1927.

So far as we have been able to discover, no one has compared the effect of hyperthyroidism with that of inanition on the weights of different organs. This we have endeavored to do in the present paper.

The facts here presented were obtained from a study of the body weights and the heart, liver and kidney weights of thirty-one normal adult dogs and nine adult dogs each of which was fed 10 Gm daily of desiccated thyroid (Armour & Co), and one dog which received 20 Gm daily, for periods ranging from thirty-two to one hundred days, all of which were kept on the same diet and under the same conditions as the normal controls. For comparison, corresponding weights have been collected from studies on inanition chiefly from Junkersdorf's laboratory.

THE EFFECT OF INANITION AND HYPERTHYROIDISM ON THE HEART

In a previous paper,⁹ we presented evidence that experimental hyperthyroidism may cause a hypertrophy of the heart, that this hypertrophy is related to the loss of body weight, being most marked in those animals which had lost from 25 to 35 per cent of body weight, and that the hypertrophy affects all of the chambers of the heart, but the left ventricle slightly more than the others. Hypertrophy of the heart in experimental hyperthyroidism in rabbits or white rats has been described by Iscovesco,¹⁰ Hoskins,¹¹ Herring,¹² Hewitt,¹³ and Cameron and Carmichael.¹⁴ Hoskins estimated that feeding thyroid caused an increase in the size of the heart to the extent of 24.6 and 16.7 per cent in old and young female rats, respectively, and 36 and 15.4 per cent in corresponding males. Herring concluded that "the increase in weight of the heart in thyroid fed (0.2 Gm daily) male rats averaged 123 per cent, and in thyroid fed females, 59 per cent." "In both male and female rats the heaviest hearts were in the animals which received most thyroid."

Jackson² cited the opinion of Lucas that the heart weight in starved dogs and rabbits is apparently normal, of Collard and Martigny, that the heart becomes atrophic in inanition, and of Kusmin that a functional hypertrophy of the heart occurs in starvation with hyperthermia. E. Voit¹⁵ concluded that the heart may lose 16 per cent of its original

9 Simonds, J. P., and Brandes, W. W. The Size of the Heart in Experimental Hyperthyroidism, *Arch. Int. Med.*, to be published.

10 Iscovesco, H. *Compt. rend. Soc. de biol.* **76** 75, 1914.

11 Hoskins, E. R. *J. Exper. Zool.* **21** 295, 1916.

12 Herring, P. T. *Quart. J. Exper. Physiol.* **11** 231, 1917.

13 Hewitt, J. A. *Quart. J. Exper. Physiol.* **12** 347, 1918-1920.

14 Cameron, A. T. and Carmichael, J. *J. Biol. Chem.* **45** 69, 1920.

15 Voit, E. *Ztschr. Biol.* **46** 195, 1905.

weight in starvation C Voit,¹⁶ however, compared that in starvation the heart suffers no loss of weight Krieger¹⁷ compared the heart weight and body weight in 123 emaciated persons and thought that the loss of heart weight was slightly less than that of the body weight in malnutrition from various causes His estimates of the loss of body weight and of heart and liver weight are shown in table 1 In Krieger's cases the estimated loss of heart weight was in all instances less (average, 9 per cent, minimum, 3.4 per cent, maximum 17.5 per cent) than the estimated loss of body weight They were more nearly equal in chronic diarrhea, in which dehydration was probably a factor of importance Levine¹⁸ believed that the heart was more or less involved in every type of malnutrition and that malnutrition is, therefore, a pathogenic factor of prime importance in various cardiovascular disorders

Witsch¹⁹ starved three dogs until they lost from 49 to 60 per cent of their original body weight, and compared the ratio of heart weight

TABLE 1—*Krieger's Estimates of the Loss of Body Weight, Loss of Heart Weight and Loss of Liver Weight Through Malnutrition from Various Causes*

Pathologic Condition	Loss of Body Weight, per Cent	Loss of Liver Weight, per Cent	Loss of Heart Weight, per Cent
Insanity	38.7	32.1	31.8
Chronic diarrhea	38.4	43.5	45.0
Malignant tumors	38.0	32.8	33.2
Chronic general infections	43.9	28.0	30.7
Tuberculosis	43.0	27.7	31.9
Old age	35.8	26.1	18.3

to final body weight in these dogs with the ratio of heart weight to body weight in eight normal dogs She concluded that no relative loss of heart weight occurred in inanition, but that an absolute loss of 42, 26.3 and 43 per cent of heart weight, respectively occurred in these three dogs Witsch was of the opinion that the heart takes part to a high degree in the atrophy of general inanition There was an increase in the water content of the hearts of the starved dogs, hence a part of the loss of heart weight was veiled She noted individual differences in the loss of weight of the starved dogs One animal starved for eighty-three days, lost 60 per cent of its body weight, but only 26.3 per cent of its heart weight

METHOD

In our experiments, we weighed the dogs at the beginning of the feeding of thyroid and at the end of the experiment These weights are designated, respec-

16 Voit, C. *Physiologie des allgemeine Stoffwechsels und die Ernährung*, in Herrmann *Handbuch der Physiologie des Gesamtstoffwechsels*, Leipzig, F. C. W. Vogel, 1881, vol. 6 p. 97

17 Krieger, W. *Ztschr. f. ang. Anat.* **7** 134, 1920

18 Levine, V. E. *Nebraska M. J.* **12** 209, 1927

19 Witsch, Kaethe. *Arch. f. d. ges. Physiol.* **211** 185, 1926

tively, original body weight (O B W) and final body weight (F B W) The hearts were removed immediately after death, the parietal pericardium was dissected away, the pulmonary artery and aorta were cut off at the upper level of the corresponding valves, all blood was removed, and the hearts were weighed The subpericardial fat was then carefully dissected away, and the heart weighed again This latter weight was the one used in our computations

The coefficients of correlation between the weight of the fat-free heart and the original and final body weights were then computed Similar correlation coefficients were computed for the body weights and the weights of the fat-free hearts of thirty-one normal dogs, obtained chiefly through the courtesy of Dr A C Ivy from acute experiments made by a class in physiology Correlation coefficients were computed for heart weights (probably not fat-free) and original and final body weights from data published by Witsch,¹⁹ Junkersdorf,²⁰ Junkersdorf and Torok²¹ and Junkersdorf and Kohl,²² in their experiments on starvation These correlation coefficients are shown in the last column of table 2

A correlation coefficient of 1 indicates that there is a perfect reciprocal relationship between the data compared, and the nearer the coefficient approaches 1 the closer is the correlation From table 2 it is seen that the correlation coefficient between heart weight and final body weight in inanition is much nearer the normal than that in hyper-

TABLE 2—*Correlation Coefficients*

Condition	Kidney Weight and Final Body Weight	Liver Weight and Final Body Weight	Heart Weight and Final Body Weight
Normal	0 9000	0 8410	0 9062
Thyrotoxicosis	0 8637	0 4620	0 8206
Inanition	0 8162	0 8901	0 9075

thyroidism, that is, the loss of heart weight in inanition more nearly corresponds to the loss of body weight than it does in hyperthyroidism This does not, however, indicate whether there is a hypertrophy of the heart in hyperthyroidism or whether it has lost a disproportionately greater or less amount of weight than the body as a whole In order to determine this point, the mean, minimum and maximum heart weight-body weight ratios of normal animals were compared with the corresponding heart weight-original body weight and heart weight-final body weight ratios in hyperthyroidism and inanition These are shown together with the mean, minimum and maximum losses of body weight, in table 3

The results shown in table 3 may be summarized as follows 1 In the group of thyrotoxic animals in which the mean loss of body weight was 31 per cent, the mean heart weight-original body weight ratio was only slightly less (77 per cent) than the normal, while in a group of

20 Junkersdorf, P Arch f d ges Physiol 200 443, 1923
21 Junkersdorf, P, and Torok P Arch f d ges Physiol 211 414, 1926
22 Junkersdorf, P, and Kohl, A Arch f d ges Physiol 211 612, 1926

starved animals in which the mean loss of body weight was 28.1 per cent the mean heart weight-original body weight ratio was considerably less (22.5 per cent) than the normal. 2 The mean heart weight-final body weight ratio in hyperthyroidism was considerably greater (31.6 per cent) than normal, while the corresponding ratio in inanition was only slightly greater (7.8 per cent) than normal. 3 The minimum and maximum heart weight-original and final body weight ratios showed

TABLE 3—*The Heart Weight-Body Weight, Liver Weight-Body Weight and Kidney Weight-Body Weight Ratios of Normal, Thyrotoxic, and Starved Dogs*

Ratios*	Normal Dogs			Thyrotoxic Dogs			Starved Dogs		
	Mean	Minimum	Maximum	Mean	Minimum	Maximum	Mean	Minimum	Maximum
H W / O B W	0.0076	0.0056	0.0098	0.0070	0.0045	0.0083	0.0039	0.0043	0.0071
H W / F B W				0.0099	0.0082	0.0119	0.0082	0.0065	0.0090
Loss B W				31.0%	14.3%	46.5%	28.1%	11.8%	49.0%
L W / O B W	0.0303	0.0183	0.0473	0.0304	0.0202	0.0364	0.0237	0.0095	0.0375
L W / F B W				0.0430	0.0326	0.0562	0.0298	0.0158	0.0480
Loss B W				31.0%	14.3%	46.5%	21.0%	11.8%	49.0%
K W / O B W	0.0057	0.0043	0.0081	0.0060	0.0045	0.0063	0.0040	0.0030	0.0051
K W / F B W				0.0085	0.0069	0.0105	0.0055	0.0040	0.0077
Loss B W				31.7%	14.3%	46.5%	25.8%	10.0%	49.0%

* H W = heart weight, L W = liver weight, K W = kidney weight, O B W = original body weight, F B W = final body weight

TABLE 4—*The Per Cent Gain or Loss in Heart Weight in Hyperthyroidism and in Inanition*

Inanition				Thyrotoxicosis			
Percentage Loss of Body Weight	Calculated Heart Weight for Original Body Weight, Gm	Actual Heart Weight, Gm	Percentage Gain or Loss of Heart Weight*	Percentage Loss of Body Weight	Calculated Heart Weight for Original Body Weight, Gm	Actual Heart Weight, Gm	Percentage Gain or Loss of Heart Weight*
11.8	77.3	72.0	-6.9	14.3	90.5	85.0	-5.60
15.0	100.0	86.0	-14.0	21.7	110.0	95.0	-13.60
20.0	151.0	132.0	-12.6	24.2	87.5	92.0	+5.15
20.7	31.0	29.0	-6.5	29.8	110.0	110.5	+0.45
23.0	21.3	18.0	-15.5	30.4	73.5	80.0	+8.80
26.0	182.5	157.5	-13.8	33.5	90.3	89.0	-1.45
27.0	113.5	92.0	-19.0	35.8	70.0	63.0	-10.00
29.5	69.5	49.0	-29.5	36.1	79.5	71.0	-10.70
43.5	117.0	79.0	-32.5	39.2	121.0	84.0	-30.50
49.0	151.0	87.9	-42.5	46.5	105.0	60.5	-42.30
50.15	151.5	87.0	-42.5				
Mean	105.0	79.0	-22.0		96.0	85.0	-11.00

* For the purposes of this table the per cent loss of heart weight was estimated by calculating the heart weight (normal ratio of H W to B W = 0.0076) for the original body weight and comparing this calculated heart weight with the actual heart weight

even more marked differences than the mean ratios. This can only mean either that the heart loses proportionately less weight in hyperthyroidism than in inanition, or that there occurs an actual relative hypertrophy of the heart in hyperthyroidism.

That this difference is related to the loss of body weight is shown in table 4.

For purposes of this table the heart weight of each animal at the beginning of the experiment was calculated by multiplying the original body weight of each animal in the thyrotoxic and starved series by the mean normal heart weight-body weight ratio of 0.0076. From this table the following facts are seen: 1. In every instance in the inanition series, the actual heart weight was less than the calculated weight, while in four of the thyrotoxic dogs, the actual heart weight was either distinctly greater or less than 1.5 per cent less than the calculated weight. These four animals had lost between 25 and 35 per cent of their body weight. 2. When the loss of body weight in hyperthyroidism reaches approximately 40 per cent or more, the loss of heart weight becomes roughly proportional to that in inanition. 3. In the starved dogs, the mean loss of heart weight was 22 per cent, or approximately 6 per cent less than the mean loss of body weight, while in hyperthyroidism, the mean loss of heart weight was only 11 per cent, or 20.5 per cent less than the mean loss of body weight.

All of the aforementioned facts seem to indicate that in experimental hyperthyroidism a relative, if not an actual, hypertrophy of the heart occurs in animals that have lost from 25 to 35 per cent of their body weight. The mechanism of this hypertrophy is not easily explained. Eyster²³ insisted that hypertrophy of the heart results from tissue injury. Although injury to the myocardium has been repeatedly demonstrated in both experimental and spontaneous hyperthyroidism (literature reviewed by Goodpasture²⁴), this does not appear to us to be a satisfactory explanation, chiefly because the response to tissue injury is an increase in the number of cells rather than in the size of the component cells. In cardiac hypertrophy, as has been shown by Karsner, Saphir and Todd,²⁵ there is an increase in the size of the heart muscle fibers without increase in their number. The theory, apparently originated by Corvisart and advocated by Cohnheim,²⁶ that increased work causes hypertrophy of the heart may apply in hyperthyroidism, but it does not explain the phenomenon. For it was shown by Wright²⁷ that in exophthalmic goiter the volume at each stroke averaged 116 cc. as compared with the normal 70 to 120 cc. at rest, and the output per minute averaged 11.7, as compared with the normal 5 to 8 liters at

²³ Eyster, J. E. A. *Experimental and Clinical Studies in Cardiac Hypertrophy*, J. A. M. A. **91** 1881 (Dec. 15) 1928.

²⁴ Goodpasture, E. W. *J. Exper. Med.* **35** 407, 1921.

²⁵ Karsner, H. T., Saphir, O., and Todd, T. W. *Am. J. Path.* **1** 351, 1925.

²⁶ Cohnheim, J. *Vorlesungen über allgemeine Pathologie*, ed. 2, Berlin, 1882,

p. 38.

²⁷ Wright, S. *Applied Physiology*, New York and London, Oxford University Press, 1926, p. 128.

rest Increased coronary flow was asseited by Rosenbach²⁸ and Thorel²⁹ to be a factor in, but not the cause of, cardiac hypertrophy, the increased coronary flow with increased nutrition followed the increased activity In hyperthyroidism with the increased output per minute, there is an increase in coronary flow and an opportunity for augmented nutrition But this is more or less counterbalanced by the shortened resting period of the heart due to the tachycardia, and by the increased metabolism

Herring¹² estimated an increase of 123 per cent in heart weight in thyroid fed male rats and of 59 per cent in females He believed that this increase could not be accounted for solely on the basis of increased metabolism, but that there was an added factor in the increased epinephrine output which he had shown occurs with thyroid feeding³⁰ In five of our dogs the adrenal glands of which were weighed the mean adrenal gland weight-final body weight ratio was 40 per cent greater than the mean adrenal gland weight-body weight ratio in twenty-two normal dogs In inanition, the adrenal glands appear to decrease in weight in about the same proportion as does the body as a whole, although some investigators found an increase rather than a decrease in the weight of these glands during starvation (review of literature by Jackson³)

While no definite explanation of the at least relative hypertrophy of the heart in hyperthyroidism is evident, it would appear that the increased coronary flow together with increased work may be important factors

THE EFFECT OF HYPERTHYROIDISM AND INANITION ON THE LIVER

The liver weight-body weight ratio is not constant because this organ is a storage depot for protein, fat and glycogen Schondorf³¹ found that the liver weight-body weight ratio of dogs fed a high carbohydrate diet was 0.0640 Profitlich³² found that on a high protein diet this ratio was 0.0350, and Gross,³³ that it was 0.0417 Gerhartz³⁴ pointed out that this ratio also varies with the age of the dog in the first week of life, it was 0.0390, in the second week, 0.0430, in the thirty-fourth week, 0.0364, in adult dogs, 0.0265 Junkersdorf²⁰ found the normal ratio to be 0.0300

28 Rosenbach, O Arch f exper Path u Pharmacol **9** 1, 1878

29 Thorel, Charles Ergebn d allg Path u path Anat **17** 90, 1915

30 Herring, P T Quart J Exper Physiol **11** 47, 1917

31 Schondorf Arch f d ges Physiol **99** 191 1903

32 Profitlich Arch f d ges Physiol **119** 465, 1907

33 Gross Verhandl d deutsch path Gesellsch **21** 196, 1926

34 Gerhartz, H Arch f d ges Physiol **135** 160, 1910

In our series of thirty-one normal dogs, the mean liver weight-body weight ratio was 0.0303 (table 3)

Jackson² quoted Bidder and Schmidt and Bourgeois to the effect that the liver loses weight in starvation more rapidly than the body as a whole, a conclusion in which Jackson³⁵ himself concurred. Junkersdorf³⁶ found that the liver lost weight more rapidly than the body in dogs fasting eleven days, and that this loss was roughly proportional, with individual variations, to the loss of body weight and to the original glycogen content of the liver. E. Voit³⁷ asserted that the liver may lose 50 per cent of its weight during starvation. Pflüger³⁸ and Schondorf³⁹ each starved dogs for twenty-eight days and found that the liver weight-body weight ratio was 0.0150 and 0.0194, respectively. Witsch¹⁹ concluded that the liver had lost 22 per cent of its weight in three dogs which had been starved until they had lost 49, 50 and 60 per cent, respectively, of their original body weights. She concluded that loss of glycogen accounts for practically the entire reduction in dry substance in the livers of these dogs. There was an actual increase of fat. She did not agree with C. Voit⁴⁰ and Awrorow⁴¹ that the liver actually increases in weight at the expense of other organs during starvation. Rous and McMaster⁴² came to the tentative conclusion that a comparison of the weight of the liver with that of the soft parts of the body shows that, relatively, the liver is three fourths as large in a rat suffering from extreme inanition as in a well nourished rat. In their series, the mean loss of body weight was 33.9 per cent, while the mean loss of liver weight (liver weight calculated for original body weight with use of 0.0410 as the normal ratio for rats) was 53.2 per cent.

In Krieger's¹⁷ series of 123 cases of inanition in man (table 1), the estimated average loss of liver weight was 9.6 per cent less than the estimated average loss of body weight.

Hoskins¹¹ and Hewitt¹³ asserted, as a result of their experiments on rats, that hypertrophy of the liver occurs during the feeding of thyroid. The former calculated that the increase in absolute liver weight was 26.7 and 30.5 per cent in older and younger females, respectively, and 24.4 and 6.4 per cent in older and younger males.

35 Jackson, C. M. *Am J Anat* **18** 75, 1915

36 Junkersdorf, P. *Am J Anat* **186**:238, 1921

37 Voit (footnote 15, p. 167)

38 Pflüger, E. *Arch f d ges Physiol* **119** 117, 1907

39 Schondorf, B. *Arch f d ges Physiol* **67** 438, 1897

40 Voit, cited by Witsch (footnote 19)

41 Awrorow, cited by Morgulis (footnote 1)

42 Rous, P., and McMaster, P. D. *J Exper Med* **39** 425, 1924

In our experiments, the liver was removed immediately after death before the blood had coagulated. It drained out rapidly while the diaphragm and gallbladder were being dissected off. Hence the blood content of these livers was reduced to a minimal and comparable amount.

The coefficient of correlation between liver weight and body weight (column 3, table 2), is not as great as those of correlation between heart and kidney weights and body weight. This is, as already pointed out, probably due to the variations in the quantity of stored material in the liver due to variations in the diet of the animal. In inanition, the correlation between liver weight and final body weight was greater than the normal, while in thyrotoxicosis it was so low as to suggest that there is practically no correlation between these weights. The

TABLE 5—*The Difference Between the Actual Weight of the Liver and the Weight Calculated for the Final Body Weight*

Dog	Days of Thyroid Feeding	Original Body Weight, Kg	Final Body Weight, kg	Per Cent Loss of Body Weight	Actual Liver Weight, Gm	Calculated Liver Weight for Final Body Weight,* Gm	Per Cent Difference Between Actual and Calculated Liver Weight
1	48	11.9	10.2	14.3	397	312	+21.4
2	49	14.5	11.35	21.7	382	341	+9.9
3	57	11.6	8.8	24.2	300	267	+31.5
4	93	14.6	10.25	29.8	398	313	+21.5
5	82	9.7	6.75	30.4	301	190	+36.6
6	32	11.9	8.04	33.5	435	243	+44.0
7	70	9.2	5.9	35.8	200	179	+31.0
8	57	10.5	6.7	36.1	360	204	+43.5
9	91	15.85	9.65	39.2	317	291	+7.3
10	100	13.9	7.39	46.5	415	224	+46.2
Mean—thyrotoxicosis				31.0	362	255	+26.0
Mean—inanition				21.0	229	216	-12.0

* The figures in this column were obtained by multiplying the final body weight in grams by 0.303, the normal ratio between body weight and liver weight.

reason for this lack of correlation is evident in table 3, where it is seen that the mean normal liver weight-body weight ratio is 0.0303, while the mean liver weight-final body weight ratio in inanition is 0.0298 and in thyrotoxicosis is 0.0430.

In our series of thyrotoxic dogs, the actual liver weight was in every instance greater than the liver weight calculated for the final body weight, as is shown in table 5. The mean difference was 26 per cent greater, although the mean loss of body weight was 31 per cent, while the mean difference in inanition was 12 per cent less in a group of dogs in which mean loss of body weight was 21 per cent.

In table 6 is shown the per cent gain or loss in liver weight in inanition and thyrotoxicosis. In this table, the liver weight was calculated by multiplying the original body weight by the normal ratio of 0.0303. In inanition, the actual liver weight was less than the calculated weight in all except one animal, which had lost 14 per cent of its body weight, in the thyrotoxic series, the actual liver weight was greater

than the calculated weight in five of the ten animals studied. In thyrotoxicosis, there was a mean loss in liver weight of only 0.475 per cent although the mean loss of body weight in these animals was 31 per cent. In inanition, the mean loss of liver weight was 30 per cent, while the mean loss of body weight was 21 per cent. From these figures it is seen that in thyrotoxicosis the liver does not lose weight in the same proportion as the body as a whole, while in starvation, the liver, so far as these figures go, loses weight in greater proportion. This is in harmony with Jackson's³⁵ view which we have quoted. This is

TABLE 6—*The Per Cent Gain or Loss of Liver Weight in Inanition and Thyrotoxicosis*

Inanition				Thyrotoxicosis			
Per Cent Loss of Body Weight	Calculated Liver Weight for Original Body Weight,* Gm	Actual Liver Weight, Gm	Percentage Gain or Loss of Liver Weight	Per Cent Loss of Body Weight	Calculated Liver Weight for Original Body Weight * Gm	Actual Liver Weight, Gm	Percentage Gain or Loss of Liver Weight
14.0	215.0	237.5	+10.5	14.3	362.0	397.0	+9.7
14.6	227.5	176.0	-22.6				
21.5	264.0	153.5	-42.0	21.7	438.0	332.0	-12.8
21.0	188.0	187.5	-0.03				
24.5	233.0	159.0	-31.5	24.2	350.0	390.0	+11.4
25.0	158.0	131.5	-16.8				
28.5	182.0	160.5	-11.8	29.8	440.0	398.0	-9.5
29.0	222.0	191.5	-13.8				
29.3	280.0	150.0	-46.5				
35.0	204.0	131.0	-35.7	30.4	295.0	301.0	+2.05
				33.5	358.0	435.0	+21.5
				35.8	277.0	260.0	-6.2
				36.1	315.0	360.0	+14.3
				39.2	480.0	317.0	-34.0
43.5	470.0	145.0	-69.0	46.5	420.0	415.0	-1.2
49.0	612.0	245.0	-60.0				
Mean	270.8	175.0	-30.0		376.0	372.0	-0.475

* The figures in these columns were obtained by multiplying the original body weight in grams by 0.0303, the normal ratio between body weight and liver weight.

shown even more clearly in table 7 in which the mean, minimum and maximum liver weight-original and final body weight ratios are compared with the corresponding ratios for normal animals. Here it is seen that the mean liver weight-original body weight ratio in thyrotoxic dogs was 0.03 per cent greater, while in inanition it was 22 per cent less than the normal liver weight-body weight ratio. In thyrotoxicosis, the mean liver weight-final body weight ratio was 42 per cent greater, and in inanition 17 per cent less, than the normal. The same differences are evident in the minimum and maximum ratios, except in the case of the maximum liver weight-original body weight ratio.

Witsch¹⁹ concluded that the loss of liver weight in starvation could be accounted for by the loss of glycogen. Feeding thyroid also causes complete or almost complete loss of glycogen from the liver as shown

by Schryver,⁴³ Cramer and Krause,⁴⁴ Parhon⁴⁵ and Fukui.⁴⁶ Hence, since in thyrotoxicosis there is practically no actual loss of liver weight, something must occur in this organ to counterbalance this loss of glycogen. Just what this is we are not at present prepared to state. Rous and McMaster⁴² concluded that the changes which occur in the liver during fasting are essentially conditioned by functional demands made on the liver. With the markedly increased metabolism in hyperthyroidism, it is probable that the functional activity of the liver is greatly increased. This increased activity may take one or both of two directions. In the first place, it is well known that in hyperthyroidism there is a marked increase in the excretion of urea in the formation

TABLE 7—*The Per Cent Difference Between Liver Weight-Body Weight Ratios in Normal, Thyrotoxic, and Starved, Dogs*

Ratios Compared [†]	Thyrotoxicosis		Inanition	
	Per Cent Difference*	Percentage of Loss of Body Weight	Per Cent Difference*	Percentage of Loss of Body Weight
Mean L W / Δ B W †				
Mean L W /O B W	+ 0.03	31.0	-22.0	21.0
Mean L W / Δ B W				
Mean L W /F B W	+ 42.0	51.0	- 1.7	21.0
Minimum L W / Δ B W				
Minimum L W /O B W	-10.4	59.2	-48.0	43.5
Minimum L W / Δ B W				
Minimum L W /F B W	-78.0	39.2	-13.6	20.0
Maximum L W / Δ B W				
Maximum L W /O B W	-23.0	33.5	-20.7	21.0
Maximum L W / Δ B W				
Maximum L W /F B W	+18.8	46.5	+ 1.5	25.8

* The figures indicate the degree to which the second ratio in each pair is greater or less than the first or normal, ratio.

† L W = liver weight, Δ B W = normal body weight, O B W = original body weight, F B W = final body weight.

of which the liver plays the chief rôle, as shown by Bollman, Mann and Magath.⁴⁷ In the second place, the increased metabolism of hyperthyroidism calls for an increase of available and utilizable carbohydrate for energy requirements. The liver is depleted of its glycogen, and the blood sugar is not increased because it is burned at such a rapid rate. Cramer⁴⁵ considered glycogen as a specific product of secretion of liver cells. The glycogenic function of the liver is, he thought, an autonomous secretory function by which the liver produces carbohydrate in the form of glycogen independently of any supply of preformed

43 Schryver, S. B. *J. Physiol.* **32**, 159, 1905.

44 Cramer, W., and Krause. *Proc. Roy. Soc., series B* **86**, 550, 1913.

45 Parhon, M. *J. de physiol. et de path. gen.* **15**, 75, 1913.

46 Fukui, T. *Arch. f. d. ges. Physiol.* **210**, 410, 1925.

47 Bollman, J. L., Mann, F. C., and Magath, T. B. *Am. J. Physiol.* **69**, 371, 1924.

48 Cramer, W. *Brit. J. Exper. Path.* **5**, 128, 1924.

carbohydrate in the food and secretes it into the blood in the form of dextrose. Stimulation of the glycogenic function of the liver by the thyroid and suprarenal hormones leads in the normal organism to increased oxidation of carbohydrates, increased formation of carbohydrates from protein, increased heat production and increased nitrogen excretion. If Cramer's idea is correct, there is a marked increase in the functional activity of the liver in the production of utilizable carbohydrate, which is oxidized so rapidly that it does not accumulate in the liver as glycogen nor in the blood as dextrose. Further indication of increased activity on the part of the liver in hyperthyroidism is evidenced by the finding of impairment of liver function in twenty-two of forty-four cases of thyrotoxicosis by Youmans and Warfield⁴⁹. This impairment was in some degree associated with loss of body weight.

This increased functional activity and the increased rate of blood flow are probably important factors in the failure of the liver to lose weight in proportion to the body as a whole in hyperthyroidism. This may, perhaps, be considered a relative, if not an actual, hypertrophy.

THE EFFECT OF THYROTOXICOSIS AND INANITION ON THE KIDNEYS

In his monograph, Jackson² quoted Carville and Bochefontaine (1875), Luciani and Bufalini (1882) and Falck (1875) to the effect that in starvation the kidneys are small and atrophic. In his later work, Jackson³⁵ asserted that in inanition the kidneys lose weight relatively somewhat less than the body as a whole, thus gaining in relative weight; but in absolute weight, the kidneys lost 25.5 per cent in acute inanition and 26.8 per cent in the chronic form. Witsch¹⁹ observed a relative increase in kidney weight in the three dogs which she had starved until they lost from 49 to 60 per cent of their original body weight.

Hewitt¹³ and Hoskins¹¹ asserted that the feeding of thyroid to rats causes hypertrophy of the kidneys. Hoskins calculated that there was an increase in absolute weight of 46.3 and 33 per cent, respectively, in older and younger females, and 44.4 and 40.4 per cent in corresponding males.

There is a fairly close correlation between body and kidney weight in normal dogs, as may be seen in column 2 of table 2. In starvation, the coefficient of correlation is slightly greater than normal, while in thyrotoxicosis it is considerably less. This indicates that in starvation the kidneys lose weight in about the same proportion as the body as a whole, while in thyrotoxicosis there is a disproportionate loss of weight in either the kidneys or the body.

⁴⁹ Youmans, J. B., and Warfield, L. M. Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, *Arch Int Med* **37** 1 (Jan.) 1926.

Table 3 shows that in thyrotoxicosis the mean kidney weight-original body weight and final body weight ratios are both greater than the normal, while in inanition both ratios are less than normal. This indicates that in thyrotoxicosis the kidneys do not lose weight in the same proportion as the body.

TABLE 8—*The Per Cent Difference Between the Actual Kidney Weight and the Kidney Weight Calculated for the Final Body Weight*

Dog	Days of Thyroid Feeding	Original Body Weight, Kg	Final Body Weight, Kg	Per Cent Loss of Body Weight	Actual Kidney Weight, Gm	Calculated Kidney Weight for Final Body Weight,* Gm	Per Cent Difference Between Actual and Calculated Kidney Weight
1	48	11.0	10.2	14.3	71.0	68.0	+18.3
2	49	11.7	11.95	21.7	83.5	65.0	+21.3
3	82	9.7	6.75	30.4	63.0	38.5	+38.7
4	92	11.9	8.04	33.5	72.5	46.0	+35.3
5	70	9.2	5.7	35.8	62.0	36.0	+41.7
6	57	10.5	6.7	36.1	66.5	38.5	+42.0
7	91	15.85	9.65	39.2	74.5	55.0	+25.5
8	100	13.9	7.4	46.5	62.5	42.5	+32.0
Mean—thyrotoxicosis				31.7	69.0	47.5	+32.5
Mean—inanition				25.6	50.7	62.5	-12.0

* The figures in this column were obtained by multiplying the final body weight by the normal kidney weight/body weight ratio of 0.0057.

TABLE 9—*The Per Cent Gain or Loss in Kidney Weight in Thyrotoxicosis and Starvation*

Inanition				Thyrotoxicosis			
Per Cent Loss of Body Weight	Calculated Kidney Weight for Original Body Weight,* Gm	Actual Kidney Weight, Gm	Percentage Gain or Loss of Kidney Weight†	Per Cent Loss of Body Weight	Calculated Kidney Weight for Original Body Weight,* Gm	Actual Kidney Weight, Gm	Percentage Loss or Gain in Kidney Weight†
10.0	56.0	39.0	-30.0	14.3	67.5	71.0	+5.2
15.2	75.0	61.5	-17.3	21.7	82.5	83.5	+1.2
17.3	137.5	124.2	-11.1	30.4	55.0	63.0	+14.6
19.0	92.5	53.0	-42.5	33.5	68.0	72.5	+4.5
20.0	114.5	61.1	-44.0	35.8	52.5	62.0	+18.0
20.5	45.5	33.3	-26.7	36.1	60.0	66.5	+10.5
20.7	28.5	15.7	-39.4	39.2	90.5	71.5	-17.7
21.8	122.0	69.8	-42.5	46.5	79.5	62.5	-21.5
29.3	62.5	39.0	-25.7				
36.7	85.5	77.0	-10.0				
43.2	88.0	63.2	-28.0				
49.0	114.0	59.3	-47.5				
Mean	83.0	58.2	-29.9		69.4	69.1	+1.3

* The figures were obtained by multiplying the original body weight by the normal kidney weight/body weight ratio of 0.0057.

† For the purposes of this table, the per cent gain or loss of kidney weight was estimated by calculating the kidney weight (normal KW/BW ratio = 0.0057) for the original body weight. This calculated kidney weight was compared with the actual kidney weight in each animal in the series.

In table 8 the kidney weight calculated by multiplying the final body weight by the normal ratio 0.0057 is seen to be less than the actual kidney weight in every one of the eight animals studied. The mean per cent difference in the last column of the table shows that the actual kidney weights of the series were 32.5 per cent greater than the cal-

culated weights, although the mean loss of body weight for the series was 31.7 per cent. A similar computation was made for a series of starved dogs data for which were collected from the literature.⁵⁰ In the starved animals, the mean actual weight was 12 per cent less than the mean calculated weight. In this series, the mean loss of body weight was 25.8 per cent.

In table 9, the difference between actual kidney weight and kidney weight calculated for the original body weight is shown. The mean actual and calculated weights in thyrotoxicosis were equal, in inanition, the mean actual kidney weight was 29.9 per cent less than the calculated weight. This indicates that the kidney weight was maintained in thyrotoxicosis in spite of the fact that there was a mean loss of body weight.

TABLE 10—*The Per Cent Difference Between Liver Weight-Body Weight Ratios in Normal, Thyrotoxic, and Starved, Dogs*

Ratios Compared	Thyrotoxicosis		Inanition	
	Per Cent Difference*	Percentage of Loss of Body Weight	Per Cent Difference*	Percentage of Loss of Body Weight
Mean K W / N B W				
Mean K W / O B W	+ 5.3	31.7	-29.7	25.8
Mean K W / N B W				
Mean K W / F B W	+49.0	31.7	- 3.5	25.8
Minimum K W / N B W				
Minimum K W / O B W	+ 4.7	46.5	-30.2	49.0
Minimum K W / N B W				
Minimum K W / F B W	+60.4	14.3	- 7.0	20.0
Maximum K W / N B W				
Maximum K W / O B W	-19.8	35.8	-35.0	36.7
Maximum K W / N B W				
Maximum K W / F B W	+29.5	35.8	-11.2	43.2

* The figures indicate the degree to which the second ratio in each pair is greater or less than the first, o. normal, ratio.

of 31.7 per cent, while in starvation there was a mean loss of approximately 30 per cent in kidney weight in a series of dogs whose mean loss of body weight was only 25.8 per cent.

In table 10, the mean, minimum and maximum kidney weight-original and final body weight ratios are compared with the corresponding normal ratios. From this table it may be seen that the mean kidney weight-original body weight ratio was 5.3 per cent greater in thyrotoxicosis, and 29.7 per cent less in inanition, than the normal ratio. The mean kidney weight-final body weight ratio in thyrotoxicosis was 49 per cent greater and in starvation 3.5 per cent less, than the normal mean ratio. Much the same differences are shown in the minimum and maximum ratios.

This apparent relative hypertrophy of the kidneys is, perhaps, explainable on the same basis as the apparent relative hypertrophy of

⁵⁰ Junkersdorf et al (footnotes 20, 21, 22)

the heart and liver, namely, increased work (excretion of an excess of urea and other products of augmented metabolism) and increased blood flow (increased volume per stroke and output per minute of the heart)

COMMENT

From the data presented it appears that in starvation the heart and kidneys lose weight in about the same or slightly less proportion than the body as a whole, while the liver loses in distinctly greater proportion. This corresponds with Hayashi's conclusion (cited by Jackson³) that in inanition the heart and kidneys lose weight more slowly, and the liver more rapidly than the body. In thyrotoxicosis there appears to be a hypertrophy, relative or actual, in all three organs.

Witsch¹⁰ believed that the incongruity between the relative weights of the liver under physiologic conditions and in hunger inanition is due to the fact that the skeleton takes little part, only about 5 per cent, in the loss of body weight in inanition. Rous and McMaster⁴² stated that a comparison of the liver weight in mice with that of the soft body (net body weight less the weight of the ligamentous skeleton) brings out the fact that the organ is, relatively speaking, three fourths as large at extreme inanition as in the well nourished animal. We did not dissect away the soft parts in our animals and weigh them separately. However, E. Voit⁴⁷ calculated that in a well nourished dog the skeleton constitutes 15 per cent of the body weight and in starvation 23 per cent. Using these figures we calculated the original and final soft body weights for each animal in the starved and thyrotoxic series and for the normal dogs, and then calculated the ratios of the organ weights to the soft body weights and compared them with the corresponding normal ratios. The actual ratios were different, but the comparative results differed so slightly from those given that it has not been thought worth while to record them in detail.

In starvation, the animal is deprived of all food, the metabolic rate is lowered, except for the slight increase in the initial days described by Kunde,⁵¹ and the animal becomes inactive. In experimental hyperthyroidism, on the other hand, the dog takes the normal amount or even an excess of food, the metabolic rate is increased, and the animal is hyperactive. One would be warranted, therefore, in presupposing a difference in the part played by individual organs in the general loss of body weight in hyperthyroidism and inanition, respectively. The facts presented bear out this *a priori* supposition.

The apparent relative, if not absolute, hypertrophy of the heart, liver and kidneys in hyperthyroidism is explained, perhaps, by the same causes in the case of each organ, namely, increased function and aug-

51 Kunde, Margaret M. Am J Physiol 63:401, 1922-1923

mented blood flow through the organ. The thyroid gland in these animals was in every case small, and this organ certainly was not called on for increased functional activity under the conditions of these experiments, although the blood flow through it was probably increased just as it was through other organs of the body. Hence it would seem that both increased function and increased nutrition are essential factors in hypertrophy.

In inanition there is decreased activity and decreased function of most of the organs, including the heart. In this condition, therefore, the two chief factors in hypertrophy of an organ, increased function and increased nutrition, are absent. Hence the heart and kidneys, the functions of which are less reduced than those of other organs, lose weight in relatively less proportion than does the liver, and in about the same proportion, or slightly less, than the body as a whole. The liver, on the other hand, in inanition, loses its glycogen and it is not called on for increased production of urea as in hyperthyroidism. Hence the liver loses weight in greater proportion than the body as a whole in starvation.

SUMMARY

In both inanition and experimental hyperthyroidism, the animal as a whole loses weight, but the part played by the individual organ is different in the two conditions.

In starvation, the heart loses weight in about the same or somewhat smaller proportion than the body as a whole. In experimental hyperthyroidism, not only may the heart not lose weight, but in some animals it may appear to increase in size, for the actual weight after prolonged thyroid feeding may be greater than the estimated heart weight at the beginning of the experiment. This apparent hypertrophy is most definite in dogs that have lost from 25 to 35 per cent of their body weight. When the loss of body weight is 40 per cent or more, the effect of experimental hyperthyroidism on the heart appears to be about the same as that of inanition.

The effects of inanition and of experimental hyperthyroidism on the kidneys corresponds rather closely to their respective effects on the heart.

In inanition, the liver loses weight in greater proportion than the body as a whole, and this loss is closely related to the disappearance of glycogen from this organ. In experimental hyperthyroidism, the liver practically maintains its original weight in spite of its loss of glycogen.

The relative, if not absolute, hypertrophy of the heart, liver and kidneys in experimental hyperthyroidism is probably due to the combined effect of increased function and augmented blood flow in each of these organs in this condition.

VARIATIONS IN THE NUMBER OF WHITE BLOOD CELLS IN DOGS FOLLOWING ECK FISTULA*

JOHN S LAWRENCE, M D

AND

STEPHEN J MADDOCK, M D

Fellow of the National Research Council in the Department of Experimental
Surgery of the Harvard University Medical School

BOSTON

An association between the liver and the monocytes seems well established both in man and in animals. The occurrence of monocytosis in catarrhal jaundice was pointed out by Jones and Minot¹ and by Thewlis and Middleton². It has been shown also that there is an increase in the number of monocytes in the guinea-pig following the subcutaneous injection of yellow phosphorus³. Lawrence and his associates⁴ recently published data to show that following experimental, complete biliary obstruction in dogs and in guinea-pigs there is only a slight increase in the number of circulating monocytes, whereas the number of these cells is more definitely increased following partial biliary obstruction, as was previously found by Holt⁵. We have unpublished data indicating that coal tar in doses sufficient to cause marked hepatic lesions does not produce an increase in the number of circulating monocytes in the rabbit. Additional data on hand tend to show that massive doses of sulpharsphenamine and carbon tetrachloride do not cause increases in the number of monocytes in guinea-pigs even though the livers of the animals may show appreciable lesions. In brief, the relationship between the liver and the circulating monocytes has been studied

* Submitted for publication, Sept 5, 1929

¹ From the Thorndike Memorial Laboratory of the Boston City Hospital and the Department of Medicine, Harvard Medical School

1 Jones, C M, and Minot, G R. Infectious (Catarrhal) Jaundice. An Attempt to Establish a Clinical Entity, Observations on the Excretion and Retention of the Bile Pigments, and on the Blood, Boston M & S J **189** 531, 1923

2 Thewlis, Ethel, and Middleton, W S. The Leukocytic Picture in Catarrhal Jaundice (Cholangitis), Am J M Sc **169** 59, 1925

3 Lawrence, J S, and Huffman, M M. An Increase in the Number of Monocytes in the Blood Following Subcutaneous Administration of Yellow Phosphorus in Oil, Arch Path **7** 813 (May) 1929

4 Lawrence, J S, Huffman, M M, Jones, Edgar, Maddock, S J, and Nowak, S J G. Variations in the White Blood Cells Associated with Experimental Obstructive Jaundice, to be published in the March issue

5 Holt, R B. Effect on White Blood Cells in Rabbit by Ligation of Common Bile Duct, Proc Soc Exper Biol & Med **24** 974, 1927

clinically in a series of patients with jaundice of various types and experimentally in animals by means of injection of liver intraperitoneally, by treatment with various substances known to be toxic to the liver, and by production of complete and partial biliary obstruction. An increase in the number of circulating monocytes has been found following the injection of phosphorus subcutaneously and of liver intraperitoneally and also in biliary obstruction. The most striking instances of this were found in animals treated with phosphorus.

The next general mode of attack on the problem has been by changes in the vascular supply to the liver. A series of dogs has been studied as regards their white blood cell formulas following the production of Eck fistula with and without splenectomy and also following reverse Eck fistula. Simple Eck fistula has been associated with marked increases in the number of circulating monocytes. Splenectomy combined with Eck fistula has produced less striking increases in the number of monocytes, whereas reverse Eck fistula has been associated with increases of about the same degree as those found following control operations of various sorts.

METHODS

The data reported in this paper are based on observations made on twenty-one dogs, eight of which were used for control operations. One of these (dog 13) was used first as a control and later was subjected to an Eck fistula operation. Dog no. 14 was also used as a control and later for Eck fistula plus splenectomy. Unfortunately, following the second operation this animal developed septicemia and could not be included in the series of dogs on which Eck fistula and splenectomy had been done.

All differential white blood cell counts were made by the supravital method with neutral red. In practically every instance, 200 cells were counted. In a few cases, fixed preparations were made and studied with Wright's stain. A sufficient number of preliminary total and differential counts were made to establish the normal values for each dog prior to operation. In general, all blood counts for a dog were made at approximately the same time of the day. The animals were divided into the following groups:

GROUP 1—*Classic Eck Fistula*—The five animals of the group with classic Eck fistula had been operated on by the cutting string technic invented by Fischler⁶ and later modified by Fishback.⁷

GROUP 2—*Eck Fistula with Splenectomy*—The group in which Eck fistula and splenectomy had been performed consisted of four animals. The operation differed from that used for group 1 only in that at the completion of the anastomosis the spleen was removed. The splenectomy was performed by ligation of the splenic artery and later clamping and dividing of the pedicle.

6 Fischler, F, and Schroder, R. Eine einfachere Ausföhrung der Eck'schen Fistel, Arch f exper Path u Pharmacol **61** 428, 1909.

7 Fishback, F C. Anastomosis of Portal Vein with Inferior Vena Cava. A Thoroughly Tested and Satisfactory Method of Making an Eck Fistula, Ann Surg **86** 436, 1927.

GROUP 3—*Reverse Eck Fistula*—The term "reverse Eck fistula," apparently coined by Mann,⁸ refers to an operation which differs from the classic Eck fistula operation only in that the inferior vena cava is tied off cephalad to the lumbo-adrenal vein thus forcing all the blood from the rear portion of the body, as well as the portal blood, to pass through the liver. The operative technic is in other respects essentially the same as that for Eck fistula. There were five animals in this group.

GROUP 4—*Control Operations*—Eight dogs were used for control operations. In two of these, one femoral artery and vein were sewed together by a row of continuous sutures, from 5 to 6 cm long. The needle penetrated the lumina of both vessels with each stitch. One animal (dog no 20) had a single line of continuous sutures placed in the inferior vena cava so as to make a little tuck in the wall of about the same length as that necessary for the formation of an Eck fistula. Another animal (dog no 8) had the first part of the operation producing Eck fistula performed, that is, the posterior suture line was inserted as well as the cutting thread. At this point, a hole was torn in the portal vein. This was closed, the cutting thread divided and removed and the abdomen closed. Two dogs (dogs no 13 and 14) were subjected to simple laparotomies in which an abdominal incision equal in length to that used for the Eck fistula was made. The abdomen was kept open for eighty minutes (a period roughly equivalent to the average time for the production of an Eck fistula) and closed with the usual technic. The last two dogs in the group (dogs no 10 and 11) had partial ligation of both the portal vein and the inferior vena cava. In this partial ligation, suggested originally by Markowitz⁹ as a method for total hepatectomy, both vessels were tied off in such a way that about four fifths of the lumina were occluded.

Following operation, daily total and differential white blood cell counts were made for all the dogs, with a few exceptions. After the first five days following operation total and differential counts were made at varying intervals (from one to twenty-three days). The longest time that any dog was studied was 115 days (dog no 1). For this animal, twenty-seven different white cell counts were made after operation during a period of 106 days. The shortest period of postoperative study was five days (dog no 18). The smallest number of white blood cell counts and supravital differential counts after operation was five (dogs no 18 and 2). The greatest number was twenty-seven (dog no 1).

The animals were not put to death at the end of the period during which the blood was studied, but were kept alive for use in other experiments. One dog survived the Eck fistula operation for 202 days, at the end of which time it was in a moribund condition and was killed. Complete postmortem studies of the animals used in this study have not been made.

Determinations of the oxygen capacity of the blood by means of the Van Slyke method were made before and after operation in five of the dogs (dogs no 20, 13, 14, 16 and 15), and after operation in six additional dogs (dogs no 9, 8, 6, 7, 17 and 19).

A variety of types of dogs, both male and female, were used. Two pregnant dogs were included in the series. Dog no 9 gave birth to a litter of puppies fifteen days after an operation in which the femoral artery and vein were sewed together. Dog no 21 was found to have one full term viable puppy in utero at operation. This was removed by cesarean section before the reverse Eck fistula was made.

8 Mann, F. C. Studies in the Physiology of the Liver. I. Technic and General Effects of Removal, *Am J M Sc* **161** 37, 1921.

9 Markowitz, J., and Soskin, S. A Simplified Technique for Hepatectomy. *Proc Soc Exper Biol & Med* **25** 7, 1927-1928.

RESULTS

All figures, unless otherwise specified, are for the average counts made on each of the first five days following operation. The maximal number of monocytes was found in this interval in all but three instances (dogs no 4, 5 and 15). The maximal number of monocytes in dog 4 was found on the sixth day, but no blood count had been made on the fifth day. In dog no 5 there was only a slight rise in monocytes before the fifth day, but it became more definite after the sixth day. In dog no 15, the peak of the monocyte rise came on the seventh day, but there was also a definite rise during the five day period. The data for each of the groups have been collected separately.

GROUP 1—*Classic Eck Fistula*—1 The principal average operations as regards the white blood cells of this group of five dogs were. The total number of white cells per cubic millimeter increased, on the average, from 12,263 to 26,547 (116.4 per cent). The smallest increase was in dog 4, in which the preoperative total average count per cubic millimeter was 9,450 and the postoperative average total count was 11,817 (25.0 per cent). The counts for the other four dogs of the group were consistent.

2 The neutrophils increased in number tremendously, the average preoperative number per cubic millimeter being 7,833 and the average postoperative number per cubic millimeter, 20,372 (160.1 per cent). Dog 4 was the only one the count for which was not consistent, it showed a postoperative increase of only 2,254 neutrophils per cubic millimeter (from 6,376 to 8,630).

3 The eosinophils decreased in number. The greatest average percentage decrease was in dog no 4 (89.3 per cent). The maximal average decrease in actual number was in dog no 13, and was 2,789 per cubic millimeter (73.9 per cent). The average normal number per cubic millimeter for the group was 1,312, and the average postoperative number was 468, a drop of 64.3 per cent.

4 The average number of lymphocytes per cubic millimeter diminished slightly following operation (24.6 per cent), the preoperative value being 1,384 and the postoperative value being 1,043. This reaction was not constant. Two of the dogs showed practically no change (nos 1 and 15). Two others (dogs no 3 and 4) showed only a slight drop, and the remaining animal (dog no 13) had an appreciable postoperative drop.

5 There was a marked increase in the number of monocytes in the blood following operation. The average normal value per cubic millimeter for the group was 1,615, whereas the average value following operation was 4,475. This is an increase of 177.1 per cent. All the

animals of the group showed an increase in the number of the monocytes postoperatively but the greatest increases were in dogs no 1, 3 and 15, the last animal showing an increase of 284.6 per cent (from 1,695 to 6,519 per cubic millimeter). Dog no 4 was not studied on the fifth day, and had shown only a slight increase prior to this. On the sixth and seventh days however it showed an increase commensurate with the increases in the other dogs in this group. Dog no 13 had low values for monocytes throughout a period of seven days after operation, the highest value being 2,961 per cubic millimeter on the second day after operation. This dog had previously been used for a control operation in which a simple laparotomy with exposure of the inferior vena cava and portal vein was done. Blood counts were made on dog no 1 for 106 days after operation. The monocytic curve gradually returned toward the normal and by the thirty-third day had reached approximately the basic level at which it remained. The maximal level was maintained fairly constantly for fourteen days. Dog no 3 was killed on the nineteenth day after operation on account of distemper which was first noticed nine days after operation.

A on the chart shows the postoperative average percentage variations of the number of the white blood cells in the dogs in which Eck fistula operation had been performed.

GROUP 2—*Eck Fistula with Splenectomy*—The principal observations with regard to the white blood cells in the four dogs of this group were

- 1 An increase in the total number of white blood cells following operation. The average normal number per cubic millimeter was 13,293 as against 26,480 following operation (99.2 per cent). All the dogs reacted consistently in this way.

- 2 The number of neutrophils was considerably increased, the normal average per cubic millimeter being 9,202 and the postoperative average being 22,506 (an increase of 144.5 per cent).

- 3 A drop of 44.3 per cent occurred in the eosinophils the average normal value per cubic millimeter being 971 and the average postoperative value being 541. There was a well defined drop in three of the four dogs (dogs no 6, 7 and 16), but in the fourth animal (dog no 5) the average postoperative value was slightly higher than the normal. This animal however showed a marked drop in the eosinophils immediately after operation none being present in a count of 200 white cells on the second day after operation.

The number of lymphocytes decreased from 1,339 to 644 per cubic millimeter (51.9 per cent). Dog no 5 showed the smallest drop (10.4 per cent). Each of the other dogs showed an appreciable postoperative drop.

The number of monocytes increased from 1,639 to 2,595 per cubic millimeter (58.3 per cent). The greatest average percentage increase was shown by dog no. 7 (101.3 per cent), in this dog, the average normal value per cubic millimeter was 1,904, and the average postoperative value was 3,832. The highest single postoperative value for monocytes was 6,962 per cubic millimeter in dog no. 6 on the third day after operation. One of the dogs in this group (no. 16) showed an actual average diminution in the number of monocytes of 29.7 per cent.

B on the chart shows the postoperative average percentage variations in the number of the white cells of the dogs subjected to Eck fistula and splenectomy.

GROUP 3—*Reverse Eck Fistula*—The essential white blood cell observations in the five dogs of this group were:

1. There was an increase in the average total number of white cells to 89.6 per cent. The average preoperative number per cubic millimeter was 14,067, and the average postoperative number was 26,679. Each of the dogs showed an increase.

2. The number of neutrophils was increased from 9,670 per cubic millimeter before operation to 22,481 per cubic millimeter after operation. This increase was manifest in every dog.

3. A consistent postoperative diminution in the number of the eosinophils occurred, the average drop being 57.1 per cent.

4. The average value for the lymphocytes following operation was almost the same as that prior to operation, a drop of 9.6 per cent being noted. The response here was not consistent, two of the dogs (dogs no. 2 and 21) showing a definite increase and the others a diminution.

The number of monocytes per cubic millimeter increased from 1,496 before operation to 2,306 after operation (54.1 per cent). Dog no. 17 showed the greatest average percentage increase (90.3 per cent), the average preoperative number per cubic millimeter being 1,293 and the average postoperative number being 2,460. The response of the monocytes was remarkably constant in all of these animals. Only one very high value (5,408 per cubic millimeter) was noted. This occurred in dog no. 18 on the fourth postoperative day but was not maintained. The next highest value was 3,720 per cubic millimeter in dog no. 17 on the third day after operation.

C on the chart shows the postoperative average percentage variations in the number of the white cells of the dogs with reverse Eck fistula.

GROUP 4—*Control Operations*—Two of the control dogs (dogs no. 13 and 14) had had simple laparotomies performed on them. Each showed a mild postoperative leukocytosis. The average increase in the

total number of white cells was 41.8 per cent. The average increase in the number of neutrophils was 76.5 per cent. The drop in eosinophils was of the same degree as that in the dogs of the other three groups (50.8 per cent). There was practically no change in the number of lymphocytes before and after operation. The monocytes had an average value per cubic millimeter of 1,403 before operation and of 2,344 after operation. This represented an increase of 67.1 per cent. On the chart shows the average percentage variations in the number of the white blood cells of dogs after simple laparotomy.

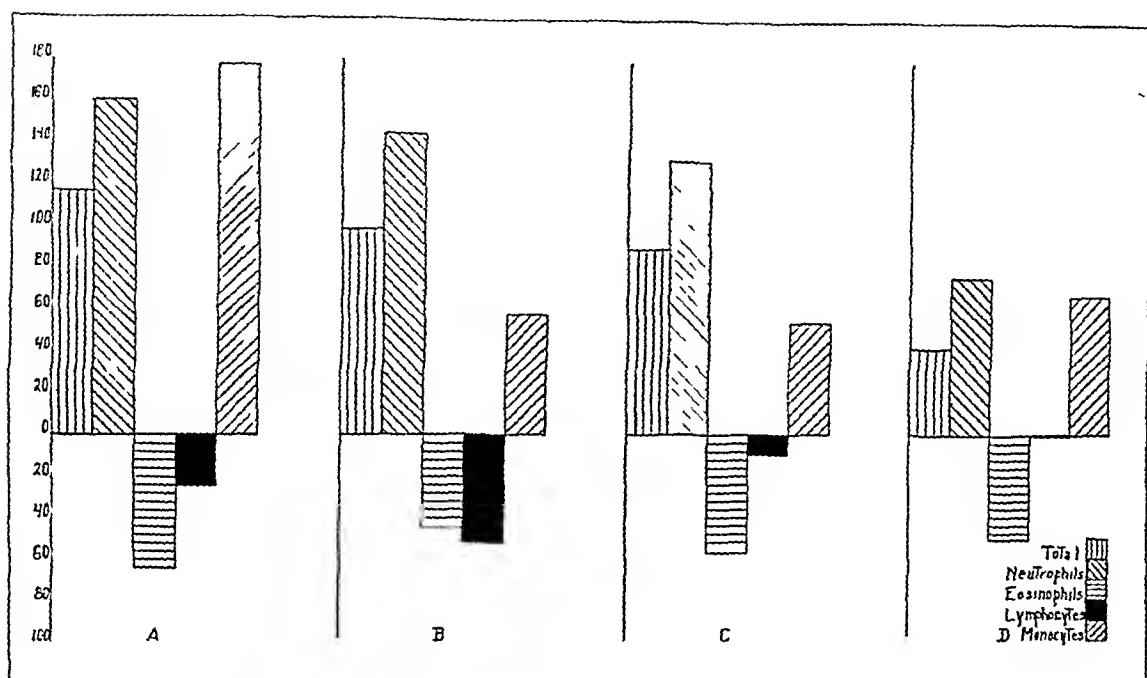
Two dogs (dogs no. 9 and 12) had a line of continuous sutures sewed between the femoral artery and vein. They showed no changes in the total or neutrophilic counts beyond normal limits. The number of eosinophils dropped 29.1 per cent. The number of lymphocytes was depressed in both dogs, the average drop being 48.9 per cent. The number of monocytes increased from 2,250 to 2,641 per cubic millimeter (17.3 per cent).

One dog (dog no. 20) had a midline incision made of the length of the usual Eck fistula. A row of continuous sutures was then placed in the inferior vena cava so as to make a little tuck in the vessel wall, but not sufficient to diminish appreciably the size of the lumen. The location of this trauma to the vessel wall was the same as that in which an Eck fistula is made. This dog showed a well marked neutrophilic leukocytosis, the total number of white blood cells being increased 102.8 per cent and that of the neutrophils 278.3 per cent. The number of eosinophils dropped 51.4 per cent and that of the lymphocytes 50.1 per cent. The number of monocytes per cubic millimeter was increased from 2,078 to 2,558 (23.1 per cent).

Two dogs (dogs no. 10 and 11) had ligatures placed around the portal vein and the inferior vena cava so as to occlude approximately four fifths of the lumina. These showed an average increase in the total white cell count of 61.1 per cent and an average increase in the number of neutrophils of 107.6 per cent. The number of the eosinophils dropped 79.1 per cent and that of the lymphocytes 27.0 per cent. Both these animals reacted alike as regards the aforesaid elements, but they differed in their monocytic responses. In dog no. 10 there was an average postoperative drop of 12.5 per cent and in dog no. 11 an average increase of 94 per cent. The highest value for monocytes in dog no. 11 was 4,862 per cubic millimeter on the second day after operation. The average value for the five days after operation was 3,649 per cubic millimeter. Both these animals had total hepatectomies later.

The remaining dog of the control group (dog no. 8) received marked intravascular trauma to both the vena cava and the portal vein. This animal showed a well marked neutrophilic leukocytosis with a tre-

mendous drop in eosinophils (89.25 per cent), a moderate drop in lymphocytes (57.7 per cent) and a rise in monocytes commensurate with that seen in dogs with Eck fistula (182.9 per cent). On account of this response, the animal was killed on the twentieth day after operation. The most interesting observation at autopsy was the gross evidence of injury to the intima of both the inferior vena cava and the portal vein. No actual blood clot was seen, but histologic section of the vessel in this area showed evidence of an old blood clot. The lymph node normally found lateral and slightly dorsal to the portal vein was somewhat enlarged and hard. There was no positive evi-



The average percentage variations in the number of white cells of dogs following different operations: *A*, following the production of Eck fistula, *B*, following removal of the spleen and the production of an Eck fistula, *C*, following production of reverse Eck fistula, and *D*, following simple laparotomy.

dence of obstruction in either vessel at this time, but the gland was so situated that it could have produced obstruction had it been swollen at any time previously.

To sum up, there was only one dog of this group of eight control animals (dog no 8) that showed an increase in monocytes of the same order of magnitude as that found in dogs with Eck fistula. This group as a whole showed less leukocytosis than the animals with either the classic or the reverse Eck fistula.

Oxygen Capacity—The average oxygen capacity for six dogs prior to operation was 22.06 volumes per cent. The average oxygen capacity for two dogs (dogs no. 13 and 15) was 22.28 volumes per cent before operation and for the same animals on the second day after operation it was 23.40 volumes per cent. An average based on one determination for dog no. 13 on the sixth postoperative day and one for dog no. 15 on the fourth postoperative day was 23.48 volumes per cent.

The preoperative oxygen capacity of dogs no. 14 and 16 averaged 23.73 volumes per cent. After these dogs had been subjected to Eck fistula and splenectomy, they showed an average oxygen capacity (one sample on the third and one on the sixth postoperative day) of 22.47 volumes per cent.

COMMENT

The most outstanding result in this series of investigations was the marked increase in the number of the monocytes per cubic millimeter of the circulating blood following Eck fistula. The response was constant in four of five animals. The fifth dog had had a previous laparotomy, which may have influenced the reaction to some extent.

Various possibilities arise when one considers the cause of this monocytic response. One of the simplest explanations is that the spleen normally adds a number of monocytes to the portal circulation, and that these are then filtered off by the liver. The recent work of Menkin¹⁰ showed that the spleen may add an appreciable number of "mononuclears" to the general circulation under the influence of short faradic stimulation. Further, Witts and Webb¹¹ reported that monocytes and lymphocytes are "much more numerous" in the splenic pulp than in the circulating blood. Hence, it seems reasonable to assume that the spleen may be partly responsible for this increase in the number of monocytes. Further, in support of the assumption are the results which we have obtained in dogs following splenectomy combined with Eck fistula. The average percentage increase in the number of circulating monocytes in the dogs of this latter group was approximately one-third that found in the dogs with Eck fistula alone. However, the response following Eck fistula and splenectomy was too irregular to allow any positive assertions to be made in regard to such a small series of animals. In conformity with the second part of the explanation, namely, the assumption that the liver normally filters off a number of monocytes from the portal blood, are the results obtained

10 Menkin, Valy. The Effect of Splenic Contraction Induced by Faradic Stimulation on the Leucocyte Level of the Splenic Vein, *Am J Physiol* **88** 737, 1929.

11 Witts, L. J., and Webb, R. A. The Monocytes of the Rabbit in B. Monocytogenes Infection. A Study of Their Staining Reactions and Histogenesis, *J Path & Bact* **30** 687, 1927.

after the production of a reverse Eck fistula. The observations in this group of animals as regards the number of circulating monocytes were remarkably constant, and, in no instance, was there a rise comparable to that found in dogs with Eck fistula. It is, of course, well appreciated that the experimental data presented herewith do not justify the presentation of the foregoing explanation in more than a purely speculative way.

Another possibility is that the spleen adds normally to the portal circulation some substance capable of causing an overproduction of monocytes, and that the action of this substance is ordinarily counteracted by passage of the substance through the liver. A similar substance might enter from any other portion of the portal system. In this connection, the question of the food and, hence, of the products of digestion present in the portal blood may be of considerable importance. It may be that only certain articles of food are associated with a marked monocytic response following Eck fistula in dogs. We have not investigated this side of the problem, since all the dogs used by us were fed with a milk and meat diet following operation. Again, changes in the structure and function of the liver after Eck fistula may cause changes elsewhere in the organism, and monocytosis might result from these changes. Removal of the spleen at the time of operation might in some way counteract the tendency to production of monocytes.

One obvious possibility in the case of the dogs with Eck fistula was that injury to the intimal wall caused the monocytic response. The five dogs with reverse Eck fistula, however, had exactly the same amount of intimal damage, but in these dogs the blood was shunted to a large extent through the liver, and it would be impossible to say that this did not counteract any tendency to monocytic response which might have occurred. That this was not the case, however, is indicated in dog no. 20, which had a laparotomy with intravascular trauma to the vena cava. There was only a slight monocytic rise in this dog, the increase being less than in two dogs with simple laparotomies. Further in support of the idea that extraportal intimal damage was not the cause of the appearance of the monocytes in increased numbers in the peripheral circulation were the results in dogs no. 9 and 12, in both of which the femoral vein and artery of one leg were traumatized without any marked rise in the number of monocytes in the blood. The marked increase in the number of the circulating monocytes in dog no. 8 seems to be explained, possibly, by the enlarged gland between the portal vein and the inferior vena cava. This may have produced some degree of obstruction to the flow of blood through the portal vein. The failure to show any increase in the number of the monocytes in one of the dogs (dog no. 10) following partial ligation of the inferior vena cava and the portal vein is additional evidence against intimal

damage being responsible for the rise in the number of the monocytes. The moderate monocytosis in the other dog with partial ligation of both veins is to be expected in such operations, as it is possible that, in this animal, obstruction to the portal blood flow may have been greater than to the flow in the vena cava, in which case we should have had a virtual Eck fistula. The evidence seems to show that intimal damage was not responsible for this reaction on the part of the monocytes.

In order to show that operation alone was not the cause of the increase in the number of monocytes, two dogs (dogs no 13 and 14) were studied following simple laparotomy. There was some increase in the monocyte count, but this increase was of about the same degree as that found in the dogs with reverse Eck fistula, and those in which Eck fistula and splenectomy had been performed. It was not comparable with that seen in the dogs with Eck fistula.

The degree of anemia was investigated by means of Van Slyke determinations of the oxygen capacity of the blood of some of the dogs. The blood for the determinations of oxygen capacity was obtained from one to eight days after operation. During this period there was only slight evidence of a drop in hemoglobin. Of course, the results obtained on the first one or two postoperative days may have been influenced by vomiting and dehydration, but results obtained at later intervals were probably not influenced by these factors. Dog no 15, which showed the highest monocytic response of any of the dogs, had an oxygen capacity of 22.53 volumes per cent before operation and one of 21.93 volumes per cent on the fourth day after operation. Therefore, the response cannot be explained by anemia. Further, if the increase in the number of the monocytes had been due to anemia, the marked response of this type should have occurred in the dogs and guinea-pigs with complete biliary obstruction reported by Lawrence and his associates.⁴

Explanation of the monocytosis as secondary to the neutrophilic leukocytosis is not possible, since the monocytic response is out of proportion to the neutrophilic. Moreover, the dogs with Eck fistula plus splenectomy and those with reverse Eck fistula had approximately the same neutrophilic leukocytosis as the dogs with Eck fistula.

The postoperative diminution in the number of the eosinophils is worthy of comment. This was constant for each group of animals. The only exception was dog no 8, in which there was a great drop (89.5 per cent). The average percentage diminution varied between 29.1 and 79.1. This result has been noted previously by Krumbhaar¹² and more recently by Lawrence and his associates.⁴ It is not a

¹² Krumbhaar, E. B. Observations on the Nature of Postoperative Leukocytosis in the Dog, *Ann Surg* 66 133, 1917.

specific response, but seems to be due to the operation. The extent and severity of the operation may have some effect on this response, as the least drop occurred in the two dogs with traumatized femoral artery and vein.

The response of the lymphocytes was in the same general direction as that of the eosinophils. There was not as much constancy in the lymphocytic reaction as there was in the eosinophilic, however. It is worthy of note that there was a greater average percentage diminution of the number of lymphocytes in the dogs with Eck fistula and Eck fistula plus splenectomy than in those with reverse Eck fistula and simple laparotomy. Since the reaction was inconstant and since there was a commensurate decrease in the number of lymphocytes in some of the control dogs (i. e., those with partial ligation of the inferior vena cava and portal vein and those with traumatized femoral artery and vein and the animal with a traumatized inferior vena cava), one must be careful in drawing any conclusions from their responses. On the other hand, the decrease in the number of lymphocytes in the dogs with Eck fistula and in those animals in which Eck fistula and splenectomy had been performed is well in accord with previous observation in patients with catarrhal jaundice.¹³

SUMMARY AND CONCLUSIONS

Monocytosis of marked degree occurs in dogs within the first week following Eck fistula. Splenectomy done at the same time as the Eck fistula tends to prevent this monocytosis. Dogs with reverse Eck fistula do not show this monocytic response. Intimal damage, anemia and operation are not the responsible factors.

A diminution of the number of eosinophils in the blood of dogs follows operations of various types on the vascular system. The average number of the lymphocytes is constantly diminished in such dogs.

Possible theoretical explanations of the monocytic response after Eck fistula are offered.

¹³ Jones and Minot (footnote 1) Thewlis and Middleton (footnote 2)

GIANT CYST OF THE ANTERIOR ABDOMINAL WALL

URACHIUS CYST OR ENTEROCYSTOMA?[†]

ANNA ALMQUIST

STOCKHOLM, SWEDEN

The case to be described forms an addition to the not great number of cases of cysts of the anterior abdominal wall which have already been discussed and classified

REPORT OF CASE

The cyst was found in a man, aged 70 who had been ill for about two years, with increasing swelling of the abdomen. He had felt only a little discomfort from it. He had grown slightly thinner. On May 1, 1928, he fell down in the street, and as he could not get up again, he was taken to the hospital.

On admission, the patient presented cardiac arrhythmia, with dull sounds, but no murmur. The respiratory organs were normal. The abdomen was greatly distended by fluid. The urine was acid and flaky. The result of the Heller test was negative.

A laparocentesis was performed, May 2. Only a few cubic centimeters of thick, brown fluid was obtained. On account of its density, the fluid did not run out.

A laparotomy was performed, May 4 (Dr. E. Edholm). After a "gridiron" incision of McBurney, one entered a cyst, from which 20 liters (20,000 cc.) of partly creamlike, partly thinly flowing, brownish-yellow fluid was tapped. This procedure was followed by extirpation of part of the cystic wall including a string-like formation.

Histopathologic Examination (Henschen)—The specimen consisted for the most part, of an irregular, dense, fibrous, hyaline, vascular and partly necrotic mass of tissue, rich in crystals of cholesterol. Here and there on the surface and in the interior could be seen simple cylindric epithelium, with goblet cells—probably enterocystoma. The string contained abundant elastic tissue and muscular fibers, cut lengthwise, it may have been an obliterated vessel.

Course—After the operation, the patient recovered temporarily, but tension gradually recurred in the cyst, which kept increasing, so that by June 5 there was a question of repeating the drainage. The general condition of the patient, however, did not allow an operation to be performed. During the final days, there was rapid deterioration. The patient died, June 6, 1928.

Clinical Diagnosis—Cysta abdominalis (enterocystoma? pancreatic cyst?), arteriosclerosis, bronchopneumonia (?)

Postmortem Examination—Autopsy was performed, June 8, by C. F. Ulfspärre. The body was that of a normally built man, the subcutaneous fat maximally reduced and the muscles somewhat reduced and weak. The skin was pale and cachectic. The thorax was flattened from the front backward to a dish shape. The abdomen was greatly enlarged, especially in its lower parts. When the chest

[†] Submitted for publication, Oct. 14, 1929.

[~] From the Pathological Department of Karolinska Institutet, Professor Folke Henschen, director.

was opened, the cavity was found to be abnormally small. The heart was dilated and weak. The myocardium was brown. Slight endocarditis was present in the mitral ostium, and moderate atherosclerosis in the valves, coronary arteries and aorta. Acute, somewhat hemorrhagic pneumonia was found in the lower right lobe. The diaphragm was greatly pushed upward, standing on a level with the third intracostal space.

When the abdomen was opened, it was difficult to find any free space in the cavity. The whole of the lower part of the abdomen was occupied by a large cyst, which was attached to the posterior sheath of the rectus muscle. In the upper part of the abdomen, the transversum was at once apparent, and was fixed to the cyst by firm adhesions. There were firm adhesions everywhere. The ileum and jejunum were much displaced, upward and backward, to the left. The colon ascendens with the cecum and the appendix lay immediately above the umbilical plane, pressed against the lateral abdominal wall. The intestines were pale and collapsed. The cyst was now isolated as far as possible. In doing this, parts of the posterior sheath of the rectus muscle were taken, too. The adhesions to the adjacent organs were cut through with sharp dissection. The wall of the cyst burst, and an attempt to close the holes by means of Péan's operation was a failure. The anterior wall was therefore cut through, and the cyst was emptied, about 6 liters (6,000 cc) at first clear yellow, later increasingly muddy, puslike, thinly flowing fluid was obtained. The cyst was taken out together with the pelvic organs and examined more closely. It consisted of a single cavity, firmly attached to the bladder. The wall was about 1 cm thick, rather dense, especially toward the bladder. The muscular coat of the bladder seemed partly to pass over directly into that of the cyst. On its interior surface, the wall was covered with flaky, greasy matter. In the upper part of the cavity, in addition to the whitish-yellow greasy coat, the wall showed knobby protuberances. The bladder, cut open, was shown to be somewhat inflamed. Somewhat to the right of the median line, in the upper part of the bladder, a little funnel-like diverticulum was found. There was hydrocele of the left testis, the right testis showed fibrous conversion. In the mucous membrane of the stomach were a number of polyps of the usual appearance. There was nothing remarkable about the pancreas. In the gallbladder were a number of gallstones, the gallbladder was shrunken, its wall thickened.

Pathologic Anatomic Diagnosis (Henschen)—*Degeneratio fusca* and *dilatatio cordis*, *endocarditis chronica verrucosa mitralis*, *cardioarteriosclerosis*, *pneumonia haemorrhagica lobi inferioris dextris*, *cysta machi*? (6,000 cc), *hydrocele testis sinistris* and *fibrosis testis dextris*, *polyposis ventriculi aliculi vesicae felleae*, *cholecystitis chronica retrahens*.

Specimens Preserved—Cyst, urinary bladder, rectum.

Macroscopic Examination—The specimen obtained at operation, by excision from the wall of the cyst, after being preserved several months in alcohol, consisted of a hard mass, in which one could distinguish only a number of irregularities on the internal wall, together with a peculiar cordlike growth about 0.5 cm thick in cross-section, which, everything taken into consideration, seemed to have been fastened at one end to the inner surface of the wall.

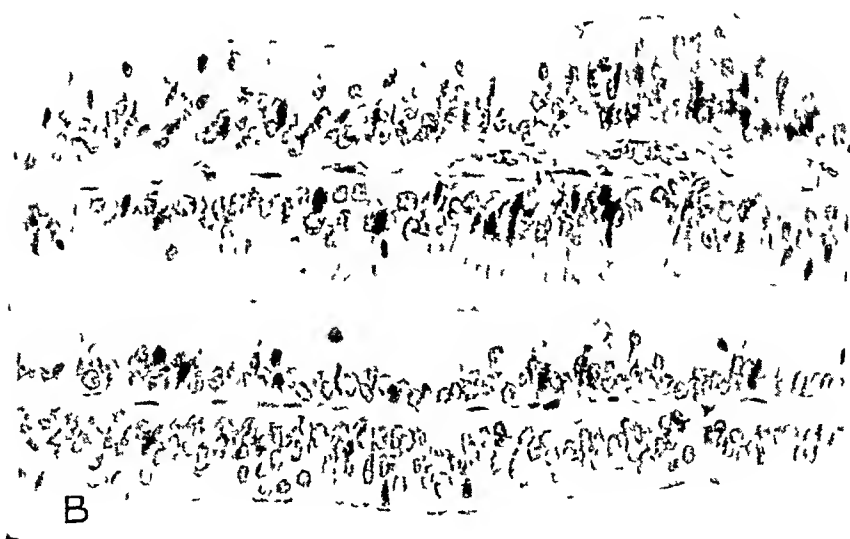
The specimens obtained at the postmortem examination, preserved in a solution of formaldehyde, were the cyst and the urinary bladder, together with the ureters, and the rectum. On closer study, the cyst was seen to be pear-shaped, its greatest diameter being about 30 cm. The rapidly narrowing point, directed caudally, was squeezed down in the median line with a funnel-like depression, between the bladder and the rectum into fossa douglasi. It ended blindly here on a level with

the upper horizontal edge of the trigonum leutaudi, corresponding in the rectum to a distance of 5 cm from the annulus haemorrhoidalis. The cyst was only loosely attached to the rectum, but was firmly fixed to the posterior wall of the bladder. The connection with the latter was still further strengthened by the powerful bundles of muscle which somewhat to the right of the median line continued from the wall of the bladder, in front of the funnel-like diverticulum of the vertex, up over the wall of the cyst. The muscular bundles were accompanied by powerful vessels. Along each side of the wall ran the two ureters. Moreover, on the wall could be seen the remnants of adhesions to the adjacent organs (see the account of the postmortem examination). The wall was from 2 to 5 mm thick, except the part just above the bladder, where the muscular coat lent it a thickness of about 1 cm. The cavity was enclosed everywhere by a dense membrane, which was coated inside with greasy matter. In the upper part, clustered together on a space of about 1 square decimeter, a multitude of papillomatous growths were found, some of them the size of pigeon's eggs, as well as a number of peculiar shreds, which were hanging loose in the cavity. On the right side, was an extensive induration which, on account of the occurrence of more abundant blood pigment, was assumed to be the scar of the operation. On the inner surface of the induration, a cartilaginous formation was found, which had a point, shooting out into the cyst's cavity. It may possibly have something to do with the "cord" that was removed by excision.

Microscopic Examination of the Specimen Obtained at the Operation—Two different sections were prepared from the wall itself, as well as one from the "cord." In one section the wall, as a whole, was clothed with mucous membrane. Here the wall was formed of loose fibrillar connective tissue, rich in nuclei and containing necrotic matter here and there. By the use of Weigert's stain for elastin, abundant elastic tissue was shown, especially in a layer immediately beneath the epithelium. The tissue was interlaced with large blood-filled vessels, and in one place much hemorrhage was seen. Small accumulations of lymphocytes were found everywhere. The mucous membrane (fig 1A) formed numerous papillae, of which a part were long and narrow, with only a thin septum of connective tissue, while others had a vascular stroma that pushed out the mucous membrane causing different formations.

The epithelium of the mucous membrane was cylindric, with goblet cells appearing abundantly here and there (fig B). It was rather irregular. Alternating with stretches of simple epithelium, areas occurred having nuclei in several layers and indications of stratified epithelium. Both in the papillae and between them were numerous glandular crypts. A number of cells had lost the typical cylindric form, this was especially the case on the vertex of many papillae, where the epithelium looked as though it had been transformed into cuboidal cells. The nuclei, generally speaking, lay near the base, and, in some places, like the rest of the cells, took an oblique position in regard to the axis of the papillae. Vacuolated cells recurred everywhere in the mucous membrane, in a number of the papillae, the connective tissue had undergone mucous degeneration. The mucous fluid between the papillae contained red blood corpuscles and leukocytes.

The other section from the wall consisted partly of a necrotic, hyaline mass of tissue, with abundant crystals of cholesterol. In the center of this mass, a hollow was seen, which was coated with epithelium of the same kind as that in the large cyst. Proliferation, however, had not been so great here, for the epithelium was more regular and the wall, with the exception of a limited space where the papillary structure reminded one of that of the large cyst, was furnished with only solitary, insignificant elevations. On the surface of the wall, the mucous mem-



A Section from the cyst wall showing various papillomatous formations
B The irregular cylindric epithelium of the papillae with goblet cells

brane remained on a little space only. In the center, it consisted of low, cylindric epithelium, which along the sides made way for cuboidal and flat epithelium, and soon ceased altogether. Whether this cavity, which was visible to the naked eye, should be interpreted as a part of the large cyst or as an independent growth must be left undecided.

The cordlike growth consisted, externally, of a layer of hyaline connective tissue with crystals of cholesterol. Inside this were plain muscular fibers enclosing a small portion of hyaline, vascular connective tissue. In the muscles, a layer of longitudinal fibers could be distinguished, and inside this, a layer of circular ones, which was abundantly interlaced with elastic tissue. On account of the almost complete absence of muscular fibers in the cyst otherwise, and because of the characteristic stratification in the cordlike growth, the latter was probably an obliterated vessel.

At the microscopic examination of the wall of the cyst as it appeared after the postmortem examination, the presence of an epithelial coat could not be seen anywhere, although sections from a large number of parts of the wall were examined. This seemed to indicate that the epithelium had completely disappeared. The papillomatous protuberances in the upper part consisted of necrotic matter, and the rest of the wall was covered with a thick layer of necrotic matter, too. The continuity of the muscular coat of the bladder and cyst, which was commented on previously, was thus confirmed by the microscope through the presence of a thick layer of longitudinal smooth muscle fibers, which were common to both organs. These, however, extended only a few centimeters up the wall of the cyst. In the other parts, no muscular fibers were to be found.

COMMENT

After the microscopic examination of the section taken at the operation, the diagnosis of probable entodermocystoma was made owing to the appearance of the epithelium. At the postmortem examination, on account of the intimate, partly muscular connection between the urinary bladder and the cyst, one arrived finally at the diagnosis *cysta urachi*. The question now is, which of these diagnoses is to be considered as having the best foundation?

It is difficult to associate the different facts brought to light, in order to formulate an explanation that can be accepted without reservation. I shall therefore present only the result I arrived at in my attempt to clear up the pathogenesis of the cyst, without making any pretension of having succeeded in solving the problem.

Naturally, the rough anatomic figure—I am thinking now especially of the muscular continuity between the bladder and the cyst—seems to speak strongly in favor of the cyst's having originated in the urachus.

The urachus appears as a ventral sinus curving out from the posterior part of the intestine, which afterward passes into the entodermal cloaca. After this has been divided in the second fetal month, by the septum urorectale, into the rectum and urogenital duct, the bladder is developed as a part of the latter. Whether the bladder, with the exception of the trigonum leutauidi, originates entirely in the cloaca or whether the urachus possibly is included in the cranial part

has not yet been established (Broman¹) The obliteration of the urachus, which sets in during the same month, is never complete, one normally finds the canal in the lower part, usually separated from the bladder by a fold Enclosing the canal and extending a bit above it, the muscular coat of the bladder continues, with preponderating longitudinal fibers in the lower third part of the urachus (Wutz²) Besides this, epithelial strands or epithelium clothed cavities are often found in the ligament, as remnants of the canal These through independent growth can assume rather considerable dimensions, they often attain a size of from 5 to 6 liters (5,000 to 6,000 cc), and in two cases, described by Cullen³ and by Freer,⁴ respectively, they had a volume of about 50 liters (50,000 cc) There has been great interest in urachus cysts during recent decades, and much has been written about them (Dossekker,⁵ Hartmann,⁶ Kohlfahl,⁷ Soulié,⁸ Weiser⁹ and many others)

Besides the cystic formation the points which the cyst now under discussion has in common with urachus cysts are the preperitoneal position between the bladder and the navel and the connection with the vertex of the bladder Why it has left the course of the urachus and pushed itself down far behind the bladder is difficult to understand Instead of wedging itself into the pelvis, it should have taken still more of the abdominal cavity, for there the resistance must have been considerably less

As may be expected, most urachus cysts are situated on the median line The reason for the lateral dislocation, which has been proved in some cases, is to be sought probably in the fact that it is not any remnants of the epithelial canal itself but sinuses of the latter that have caused the cysts Luschka¹⁰ showed that the urachus canal is "furnished with numerous larger or smaller sinuses, which lend it a

1 Broman, I Normale und abnorme Entwicklung des Menschen, Wiesbaden, J F Bergmann, 1911

2 Wutz, J B Ueber Urachus und Urachuscysten, Virchows Arch f path Anat **92** 387, 1883

3 Cullen, T S The Diseases of the Umbilicus, Philadelphia, W B Saunders Company, 1916, cited by Rankin and Parker (footnote 11)

4 Freer, A Abnormalities of the Urachus, Ann Surg **5** 107, 1887

5 Dossekker, W Klinischer Beitrag zur Lehre von den Urachuscysten, Beitr z klin Chir **10** 102, 1893

6 Hartmann, E Ueber Urachuscysten, Inaug-Diss, Halle, 1911

7 Kohlfahl, A Ein Beitrag zur Kenntnis der Urachusresten, Inaug-Diss, Giessen, 1919

8 Soulié, J Contribution a l'étude des kystes de l'ouraque, Diss, Bordeaux, 1919

9 Weiser, W R Cysts of the Urachus, Ann Surg **44** 529, 1906

10 Luschka, H Ueber der Bau des menschlichen Harnstranges, Virchows Arch f path Anat **23** 1, 1862

knotty appearance sometimes even a configuration which is reminiscent of an acinous gland'. The sinuses usually touch only a part of the wall, are more or less pedunculated and can be completely isolated. When making his extensive examinations on seventy-four cadavers Wutz found similar sinuses in nearly a third of the cases. In this way, in my case an explanation is found for the displacement of the apex of the bladder to the right. The position of the funnel-like hollow of the cyst exactly in the median line is, however, inexplicable. Possibly it may depend on the circumstance that the cyst during its wandering down into the pelvis was forced, on account of the small space there, to pursue the median line.

The difficulty of determining the genesis of the cyst now under discussion is met with in the character of the epithelium. The covering of transitional epithelium possessed by the urachus at one time recurs chiefly as transitional or flat epithelium in malformations whether this concerns fistulas, cysts or solid tumors. During recent times however, there have been some reports of cases of a neoplasm having an epithelium which bears an unmistakable likeness to the intestinal epithelium but which in every other way, points to a genesis from the urachus. Such is the case of adenoma urachi, described by Rankin and Parker,¹¹ and such are the cases of adenocarcinoma of the urachus described by Schwarz,¹² Michlin,¹³ and Kliaum.¹⁴ Schwarz placed here too, a case of tumor described by Koslowski¹⁵ under the name of navel adenoma.

Schwarz, in order to clear up the question of the occurrence of glands in the urachus, examined several urachi in numerous sections, but did not find any such tissue. Among the glands met with in the bladder, some have cylindric epithelium (Rauenbusch¹⁶). Rauenbusch collected seventy-five reports of cases of carcinoma of the bladder, of which two resembled colloid cancer of the rectum. One case, which under the name of 'bladder diverticle' has recently been sent to Professor Henschen from Serafimerlasarettet in Stockholm, presented at a microscopic examination of the somewhat inflamed mucous mem-

11 Rankin, F. W. and Parker, B. Tumors of the Urachus, *Surg. Gynec. Obst.* **42** 19, 1926.

12 Schwarz, E. Das Carcinom des Urachus, *Beitr. z. klin. Chir.* **78** 278, 1912.

13 Michlin, W. A. Zur Kasuistik der aus Resten des Ductus omphalomesentericus sich entwickelnden malignen Neubildungen, *Virchows Arch. f. path. Anat.* **209** 47, 1912.

14 Kliaum, E. Ueber primäres Karzinom des Urachus, *Wien. klin. Wchnschr.* **29** 130, 1916.

15 Koslowski, B. S. Ein Fall von wahrem Nabeladenom, *Deutsche Ztschr. f. Chir.* **69** 469, 1903.

16 Rauenbusch, L. Ueber Gallertkrebs der Harnblase, *Virchows Arch. f. path. Anat.* **182** 132, 1905.

blane, which otherwise was coated with transitional epithelium, agglomerations of transversely cut glandular ducts of the same type as those in the large intestine (As the diverticulum, as a whole, was not preserved after the operation, it was not possible to study this case more closely) In exstrophic bladders, Enderlen often saw cylindric epithelium with golbet-cells (Schwalbe¹⁷) This change in the tissue he ascribed not so much cells of a fetal character, as to adaptation caused by external irritation from the air, contact with clothing, etc This explanation does not appear to be entirely acceptable Cylindric epithelium, I suppose, must generally be considered as more fragile than transitional In chronic inflammation, the cylindric epithelium, as is well known, is not infrequently converted into transitional or flat epithelium Another explanation is more probable If, from any cause, cells belonging to an early embryonic stage are left lying about without being used for normal development into transitional epithelium, it does not seem improbable that they may follow instead the law of differentiation into intestinal epithelium (Schwarz)

If solid tumors of the urachus with cylindric epithelium are of relatively rare occurrence, a urachus cyst with cylindric epithelium is unique The adenomatous proliferation of the mucous membrane indicates, however, that in this case one is not concerned with a urachus cyst in the usual meaning, but that, if it really is a urachus malformation, it should be classified with tumors mentioned shortly heretofore Its enormous size, which gives it a resemblance of the real urachus cyst, must be ascribed to strong secretory activity on the part of the golbet-cells A diagnosis in accordance with the structure of the cyst should therefore evidently be as follows *adenocystoma papilliserium urachi*¹⁸

Enterocystomas, according to Roth,¹⁹ are "congenital sacs filled with fluid, the walls of which have, more or less completely, the structure of the intestinal canal" It was Roth who first presented these tumors systematically He separated them into two different groups (1) those which arise owing to secondary modifications in the normally disposed intestine, so that it becomes divided into several cystic formations, and (2) those which depend on a primarily abnormal development of the intestine, and which are found together with a permeable intestinal

17 Schwalbe, E Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1927

18 Tumor growth in cysts having originally normal urachus epithelium has been described by Hoffman (Flat-Cell Cancer Through Chronic Irritation of an Originally Patent Urachus, *Arch d Heilk* **11** 373, 1870), Pendl (Colloid Cancer, *Beitr z klin Chir* **91** 681, 1914), Utterstrom and Bergstrand (Ein Fall von peritonoealer Riesenzyste in der vorderen Bauchwand, *Upsala Lakareforenings forhandl Nyfoljd* **34** 1, 1928)

19 Roth, M Ueber Missbildungen im Bereich des Ductus omphalomesentericus, *Virchows Arch t path Anat* **86** 371, 1881

canal. The latter group is divided into three subdivisions (a) cysts belonging to a rudimentary twin,²⁰ (b) combined enterocystomas appearing in connection with other organic displacements (strangulated biliary ducts and numerous groups of liver-like substances,²¹ and (c) simple enterocystomas arising from abnormal diverticula of the intestine, most frequently from the diverticulum meckeli or the ductus omphalomesentericus.

Some authors assume that there must be embryonic isolation of the intestinal epithelium to cause enterocystomas, others have limited this assumption to include only the cysts arising from the ductus omphalomesentericus (Kostlivy²²).

With the atrophy which the ductus omphalomesentericus undergoes at the end of the second fetal month, different malformations can arise, owing to the total or partial persistence of the canal. If the middle part of the canal is left, enterocystomas can arise. They are generally situated on the convex side of the intestine, corresponding to the position of the ductus omphalomesentericus, they are subserous and seldom pedunculated. Following secondary displacements, they may also be met with intramesenterically. A few enterocystomas, like the cyst in question, are situated preperitoneally. Colmers,²³ who made a comparison of thirty-nine enterocystomas, found only four of this type (von Wyss,²⁴ Roser,²⁵ Schaad²⁶ and one of his own). Besides these, Dubs²⁷ reported one case. However, neither as regards the size nor as regards the relation to the bladder or urachus can points of comparison with the one under discussion be advanced.

However, the ductus omphalomesentericus and the allantois lie enclosed so near to each other in the umbilical ring that it may well be thought that a remnant of the former at its later development happened to accompany the urachus and thus gives a specious appearance of belonging genetically to the latter. In spite of the fact that Michin considered such a development of the tumor described by him as being

20 Scharer, in Klebs. Handbuch der speciellen pathologischen Anatomie, vol 1, p 1013.

21 Sanger and Klopp. Arch f Gynak, 1880, vol 16.

22 Kostlivy, S. Ein Beitrag zur Aetiologie und Kasuistik der Mesenterialcysten, Deutsche Ztschr f Chir **91** 351, 1908.

23 Colmers, F. Die Enterokystome und ihre chirurgische Bedeutung, Arch f klin Chir **79** 132, 1906.

24 Von Wyss, H. Zur Kenntnis der heterologen Flimmercysten, Virchows Arch f path Anat **51** 143, 1870.

25 Roser, W. Ueber Operation der Urachuscysten, Arch f klin Chir **20** 472, 1877.

26 Schaad, T. Ueber die Exstirpation einer Cyste des Dotterganges, Kor-Bl f Schweiz Aerzte **16** 345, 1886.

27 Dubs, J. Zur Pathologie des persistierenden Ductus omphalo-entericus, Kor-bl f Schweiz Aerzte **46** 1505, 1916.

self evident, he did not hesitate to describe the case as being cystadenocarcinoma urachi. In agreement with the theory mentioned, one should, while avoiding Michin's misleading terminology, consider the most adequate diagnosis to be that of enterocystoma.

The extension of the cyst down even into the fossa douglasi and its firm fixture there lead me, in the meantime, to touch briefly on another possibility.

May it not possibly be thought that the cyst, as it is so firmly wedged between the organs in the pelvis, may have developed just here? Certainly, in such a case it should properly be reckoned as belonging to enterocystoma, taken in the widest sense, but since with this question one enters on the sphere of urorectal fistula, it seems to me more suitable to treat of it in a special division.

It appears to me not altogether unthinkable that with the coalescence of the folds of the urorectal septum or of the septum, on one side, and of the cloacal membrane, on the other, on account of some obstruction, an epithelial germ happened to be enclosed which afterward developed further. In a similar manner, rectovesical fistulas are formed, with this difference only, that the continuity of the epithelium covering the rectum and the sinus urogenitalis within a larger or a smaller area is never broken through by the mesenchyme.

SUMMARY

In a man, aged 70, a cyst of 20 liters (20,000 cc.) was met with on the anterior abdominal wall having a plainly marked primarily muscular continuity with the bladder and a mucous membrane coated with cylindric epithelium. Three alternative diagnoses are offered in explanation of its pathogenesis: urachus cyst, enterocystoma or a cyst originating as does rectovesical fistula through an incomplete septum urorectale.

PRIMARY CARCINOMA OF THE LUNGS

IV INTRACRANIAL METASTASES *

B M FRIED, MD

AND

R C BUCKLEY, MD

BOSTON

The incidence of intracranial metastases from primary carcinoma of the lungs cannot be ascertained, for the few available statistics often fail to state whether the brain in every one of the included cases was examined. Thus Dosquet¹ in a study inspired by Lubatsch investigated the necropsy material from the institutes of pathology at Kiel and Berlin, respectively, and found metastases to the central nervous system in 33 of 105 cases of bronchiogenic carcinoma. Seyfarth² found the brain involved in 30 of 309 necropsies on patients with bronchiogenic cancer, and Levy-Simpson³ observed intracranial metastases in 19 of 139 postmortem examinations of patients with the same disease. Neither of these authors stated whether the brain was examined in every one of the necropsies of his series.

Thirty-eight proved cases of primary carcinoma of the lungs have been observed by us, and in 15 of these metastases to the central nervous system were verified either at operation or at necropsy or by both procedures. In the remaining twenty-three cases, either there was no anatomic evidence of metastases to the brain or the central nervous system was not examined. Twelve of the 15 cases were unusual in that they were diagnosed as "tumor of the brain suspects."

That the ever-increasing interest taken in the recognition of tumors of bronchiogenic origin by clinicians, roentgenologists and pathologists should be equally shared by the surgeon is due to the fact that the metastases from the small, and often symptomless, primary pulmonary

Submitted for publication, Oct 21, 1929

* From the Surgical Department of the Peter Bent Brigham Hospital

* The preceding papers of this series have been: Fried, B M: I Primary Carcinoma of the Lungs, *Arch Int Med* **35** 1 (Jan) 1925, II Further Study, with Particular Attention to Incidence, Diagnosis and Metastases to the Central Nervous System, *ibid* **40** 340 (Sept) 1927, III Histogenesis and Metaplasia of Bronchial Epithelium, *Arch Path* **8** 46 (July) 1929

1 Dosquet: Ueber die Metastasenbildung bei primären Lungen und bronchial Krebses, *Virchows Arch f path Anat* **234** 481, 1921

2 Seyfarth: Lungen Carcinome in Leipzig, *Deutsche med Wchnschr* **50** 1497, 1924

3 Levy-Simpson, S: Primary Carcinoma of the Lung, *Quart J Med* **22** 413, 1929

tumor may themselves simulate primary malignant disease. This fact is of particular importance to the neurosurgeon for, as has been observed, the tumors under discussion metastasize frequently to the central nervous system and what is more, the metastases often occur when there is no subjective evidence of the existence of a visceral tumor. It is in these instances that the metastatic tumor simulates the pre-operative life history of the most invasive and rapidly growing glioma, the glioblastoma multiforme and causes such acute intracranial symptoms as to make an intracranial operation an emergency procedure.

The purpose of this study is to discuss the clinical and pathologic observations in intracranial metastases occurring in patients with primary carcinoma of the lungs.

THE PATHWAY OF INTRACRANIAL METASTASES FROM THE LUNGS

The manner in which carcinoma of the lungs reaches the central nervous system has not previously been the object of investigation owing apparently to the fact that the frequent occurrence of this metastasis has not been noticed until recently. The subject is of interest because the spread of cancer as commonly accepted is by way of lymphatics which are lacking in the central nervous system.

The central nervous system was believed to be provided with a double set of lymphatics: (1) the lymphatic spaces of Virchow-Robin and (2) the lymphatic spaces of His.

In 1859, the French pathologist Robin⁴ found that cerebral capillaries of a certain caliber (0.33 mm in diameter) are normally separated from the cerebral tissue by a membrane that surrounds the vessel in a sleeve-like manner. He wrote that between the membrane and the capillary wall there is a space "filled with colorless granular fluid, and in people above 40 or 45 years of age with fatty granules and abundantly with an amorphous hematoin." Robin, while not assigning any special role to this space, believed it to be of importance in physiologic and pathologic conditions. Virchow⁵ also noted similar perivascular spaces "which are very expansible, forming sometimes sack-like outpocketings filled with water or with blood." Like Robin, Virchow did not attribute any definite function to these spaces. Subsequently, the latter were interpreted as lymphatics and designated as "lymphatic spaces of Virchow-Robin" (Virchow-Robinsche Lymphräume).

The lymphatic spaces described by His⁶ differ from those of Virchow-Robin in that they are outside of the latter. His, by injecting mercury into the subpial

4 Robin, C. Recherches sur quelques particularités de la structure des capillaires de l'encephale, *J. physiol.* **2** 537, 1859.

5 Virchow, R. Ueber die Erweiterung kleineren Gefässe, *Virchows Arch. f. path. Anat.* **3** 425, 1851.

6 His, W. Ueber ein perivasculars Canalsystem in den nervösen Centralorganen und über dessen Beziehungen zum Lymphsystem, *Ztschr. f. wissenschaftl. Zool.* **15** 127, 1865.

spaces found that the metal passed down into the brain by way of channels the inner wall of which was the membrane described by Robin and the outer an independent second sheath that touched the cerebral substance. More recent writers stated that the cerebral blood vessels are invested with two membranes one is that of the pia which follows the cerebral blood vessel after it has left the pia-arachnoid the other is the glial membrana limitans which separates the brain from the mesenchyme. The Virchow-Robin lymphatics are believed, then to lie between the pial membrane and the wall of the blood vessel while those of His are between the glial limiting membrane and that of the pia.

Subsequent investigations have convincingly shown that the lymphatics noted by His were artefacts due to injections of the heavy metal. Moreover the lymphatic spaces of Virchow-Robin are artificial formations and owe their existence, as do the spaces of His to injections of material from outside or probably to pathologic factors. Robin himself in a later publication reported having seen similar perivascular spaces also in the omentum.

Held⁷ stated that spaces in the central nervous system acting as lymphatics are present not outside but within the blood vessel wall i. e. between the media and the adventitia while Spielmeyer⁸ was of the opinion that the entire vascular coat is made up of lymphatic spaces. The adventitia of the cerebral blood vessels when treated with silver tannin discloses according to this author a fine reticular structure composed of intercommunicating compartments which are particularly conspicuous in disease conditions like sleeping sickness. The German workers have designated these so-called lymphatics as 'adventitial spaces of Virchow-Robin' (Virchow-Robinsche adventitielle Lymphräume).

In the cerebral blood vessels as in the visceral one notices the customary fenestration (membrana fenestrata) and also the vasa vasorum. In some pathologic processes the latter increase in number and dilate forming spaces of various size which may be interpreted as lymph channels. It would appear that lymphatics as seen at the periphery of the body are lacking in the central nervous system.

The 'body fluid' of the central nervous system is the cerebrospinal fluid extracted from the blood and filtered or possibly secreted by the choroid plexus (called by some investigators "choroid plexus gland"). From the latter through the foramen of Monro the third ventricle the aqueduct of Sylvius and the fourth ventricle and thence via the foramina it reaches the subarachnoid spaces where it is absorbed. The absorption is believed to be effected by way of the arachnoid villi into the great sagittal sinus and by way of the perineural spaces, the latter being defined as an accessory drainage. The perineural spaces convey the fluid to the tissue spaces and through the intervention of the latter it is taken up by the cervical lymphatics (Weed⁹).

In a study of a cerebral metastasis from a carcinoma of the breast, Hassin¹⁰ believed that the tumor reached the meninges via the perineural spaces in the following manner. From the periphery the new

7 Held H. Ueber die Neuroglia marginalis der menschlichen Grosshirnrinde. Monatschr. f. Psychiat. 26: 360 1909.

8 Spielmeyer W. Histopathologie des Nerven-Systems. Berlin Julius Springer 1922.

9 Weed L. H. Studies on the Cerebrospinal Fluid and Its Pathway. J. M. Research 31: 21 (Sept.) 1914. Am. J. Anat. 31: 191 (Jan.) 1923.

10 Hassin, G. Histopathology of Carcinoma of the Cerebral Meninges, Arch. Neurol. & Psychiat. 1: 705 (June) 1919.

growth reached the lymphatics of the neck and thence, via the tissue spaces, the perineural spaces "climbing" upstream to the meninges and finally reaching the brain. Other writers described the same pathway for bronchiogenic cancer.

At the present time there is a general agreement that cancer metastasizes to distant organs by way of every possible channel. Letulle and Jacquelin¹¹ produced evidence to show that the transmission of tumor from one lung to the other was effected by way of the bronchi ("métastase aérienne"). Goldmann¹² affirmed that mammary cancer is often propagated by way of the lactiferous ducts. The transmission of a carcinoma via the lymphatics, held by the older pathologists as being the essential pathway for the spread of an epithelial malignant disease, was stressed in recent years by Handley,¹³ who produced evidence to show that it is effected in two ways: (1) by permeation and (2) by transportation (cell emboli). In the first instance, tumor cells reaching the lymph vessel continue to grow within its lumen "conquering new territory" step by step. "Their driving force is an internal pressure resulting from their own proliferation," and as a rule they follow the lymph stream (orthograde "infection"). "Cancer thus spreads," said Handley, "by permeating the lymphatic system like an invisible annular ringworm." In cases in which the lymphatic channel is blocked by fibrosis or by pressure from outside, cancerous cells continue their proliferation against the lymph stream (retrograde "infection").

In the material studied by us, the bronchiogenic cancer, in all probability, reached the central nervous system by way of the blood stream.

That cancer cells are frequently present in the pulmonary vessels forming emboli therein without invading the vessel wall was noted years ago by Schmidt.¹⁴ This author also found tumor cells in the lumen of capillaries and veins, where they proliferated.

In our own investigation, tumor cells were invariably found in the lumen and walls of the blood vessels of every organ studied. The constancy of this phenomenon makes us believe that the hematogenous manner of dissemination of bronchial carcinoma is the essential one.

Goldmann showed that in experimental cancer the blood vessels undergo early pathologic changes. This is particularly marked in the veins, which show degenerative changes at the beginning of the disease.

11 Letulle, M., and Jacquelin. Les "embolies bronchiques" cancéreuses, *Presse med* **32** 825, 1924.

12 Goldmann, E. E. Studien zur Biologie der bösartigen Neubildungen, *Beitr z klin Chir* **72** 1, 1911.

13 Handley, W. S. Cancer of the Breast, New York, Paul B. Hoeber, 1922.

14 Schmidt, M. B. Verbreitungswege der Carcinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903.

The arteries resist damage for a longer time, and, as in inflammatory conditions of bacterial or toxic origin, they play for some period of time the rôle of "insulators."

Neoplastic cells aggressively invade the vascular coat, being disseminated throughout the vessel wall by way of the vasa vasorum. This is suggested by the fact that in the arteries in which nutrient vessels are particularly prominent in the outer coats, the tumor is essentially "periaarterial," while in the thin-walled veins, the new growth is seen

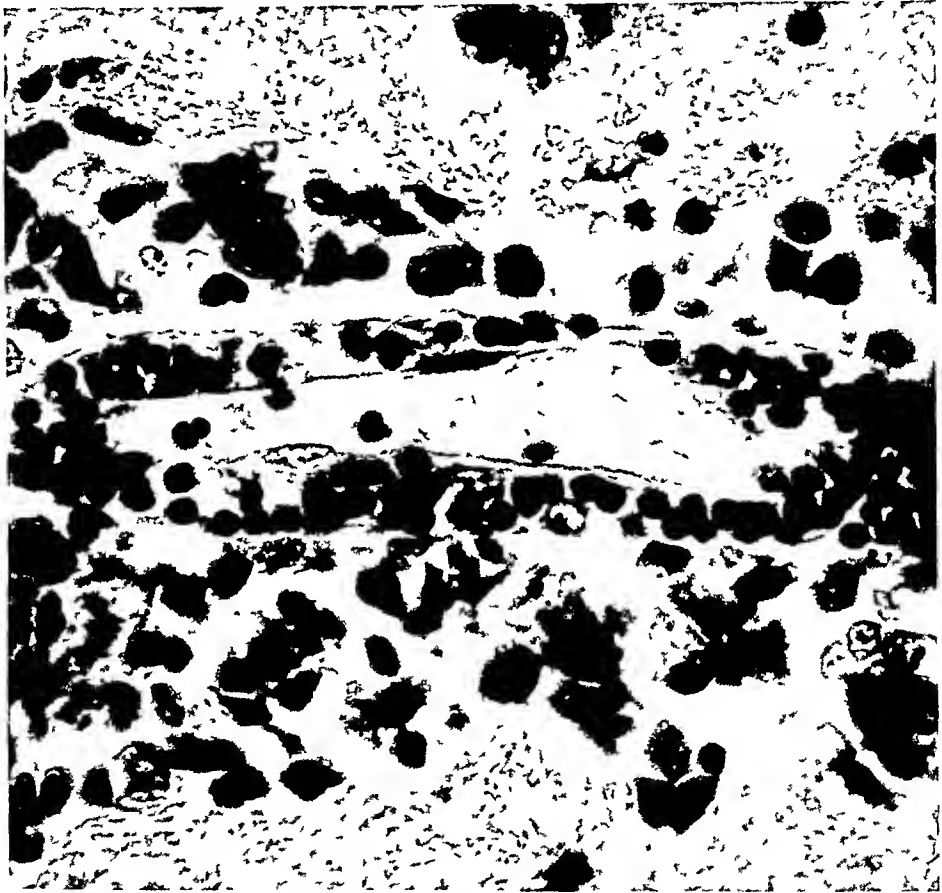


Fig 1—Dissociation of the vessel wall by lymphocytes from the blood stream with no evidence of lymphatic spaces in the vascular coat, in a case of sarcomatosis of the brain. Hematoxylin and eosin, $\times 300$

as an endophlebitis. Thus, an endophlebitis carcinomatosa is shown in figure 3, in which the cells lying free in the lumen reveal multiple mitoses. A thrombosis of a pulmonary vein by cells of a bronchiogenic cancer is demonstrated in figure 4, in which the invasion of the vascular coats by carcinomatous cells is also conspicuous. Organization of a carcinomatous thrombosis is seen in figure 5. This illustration also shows the presence of carcinomatous cells in the vascular coat and in the distended vasa vasorum. In the insert is a photomicrograph of a

thrombosed and "canalized" pulmonary vein. The canaliculi are lined by malignant epithelial cells. In such a position, neoplastic cells may remain for an indefinite period, until they ultimately reach a larger blood vessel, which they invade and thus metastasize to distant organs. The occurrence of late metastases is probably often due to a condition in which the cells are thus immured without being destroyed. The presence of cancer cells in cerebral vessels is illustrated in figures 6 and



Fig 2—Splitting of the vessel wall by invading neoplastic cells in a case of sarcomatosis of the brain. Again there are no adventitial or lymphatic spaces in the vascular coat. Eosin-methylene blue, $\times 850$.

7. Here, too, the lumen and the walls of the vessels are shown invaded by malignant cells. Finally, the distention of a few nutrient vessels by tumor cells is beautifully illustrated in figure 7.

The fact that in most instances the brain contained numerous tumor nodules invading practically every part of the hemisphere and also

the cerebellum is further evidence for the hematogenous transport of "showers" of emboli to various parts of the brain

Hematogenous metastases apparently occur either through the transmission of a single cell or a minute clump of cells or through the formation of actual tumor emboli. In both instances, as stated, secondary tumors arise that grow inside the vessels and also, by crossing the vessel wall, in the surrounding tissue.

The rather frequent occurrence of cerebral metastases in primary carcinoma of the lungs, an occurrence which is much rarer in extra-

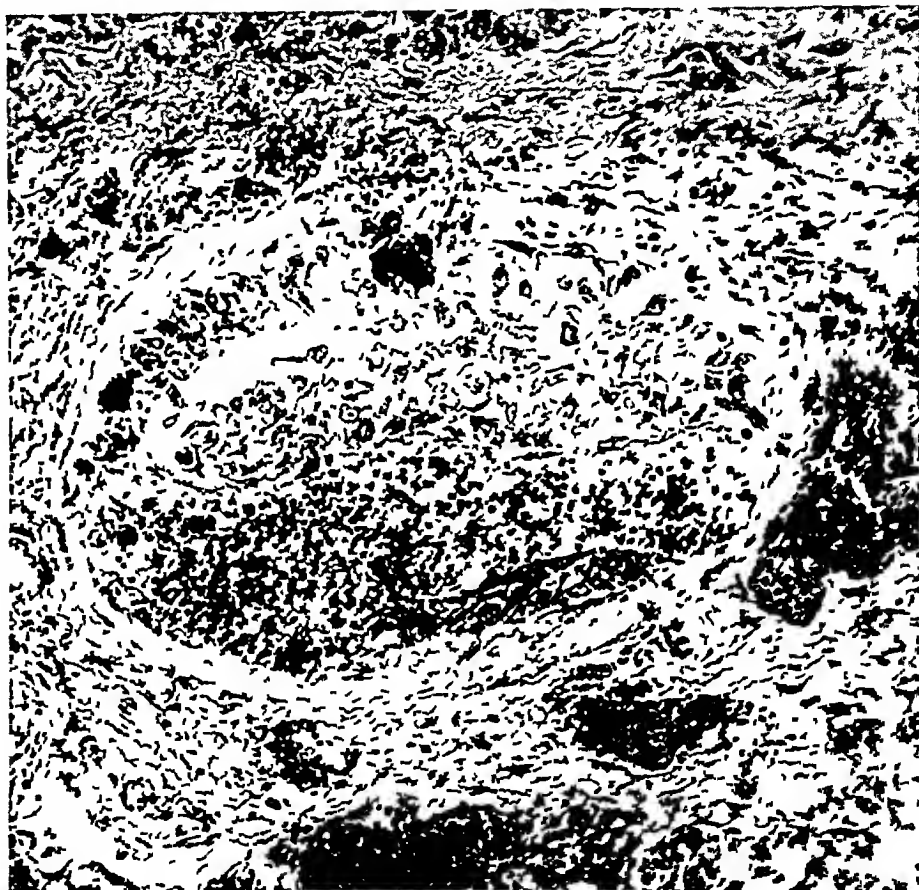


Fig 3—A section of a pulmonary vein partly occluded by a neoplastic thrombus from a bronchiogenic cancer. There is beginning organization of a thrombus of the blood cells. Eosin-methylene blue, $\times 175$

pulmonary cancer, is favored not only by the aforementioned factor, but by the absence of any barrier between the lungs and the brain. A cell embolus from a pulmonary cancer, as is clearly understood, may pass from the pulmonary vein and heart directly into the general and then into the cerebral circulation. A similar embolus from elsewhere in the body on its way to the central nervous system passes primarily through the "sieve" of the lungs, the latter serving as a barricade, thus

keeping back the advance of the growth. Visceral cancers reach the lungs with great frequency. The tumor emboli are retained, however, by the pulmonary capillaries in which they are immured. Moreover, frequently they lead to local infarct formation followed by organization and destruction of the metastatic neoplastic cells.

It is interesting that a pulmonary abscess is more often complicated by a "metastatic" cerebral abscess than are abscesses of other organs. It is likely, then, that the frequent occurrence of metastases to the brain from a pulmonary abscess and a pulmonary carcinoma is not a mere coincidence, but is due to the same underlying factor, that is, a

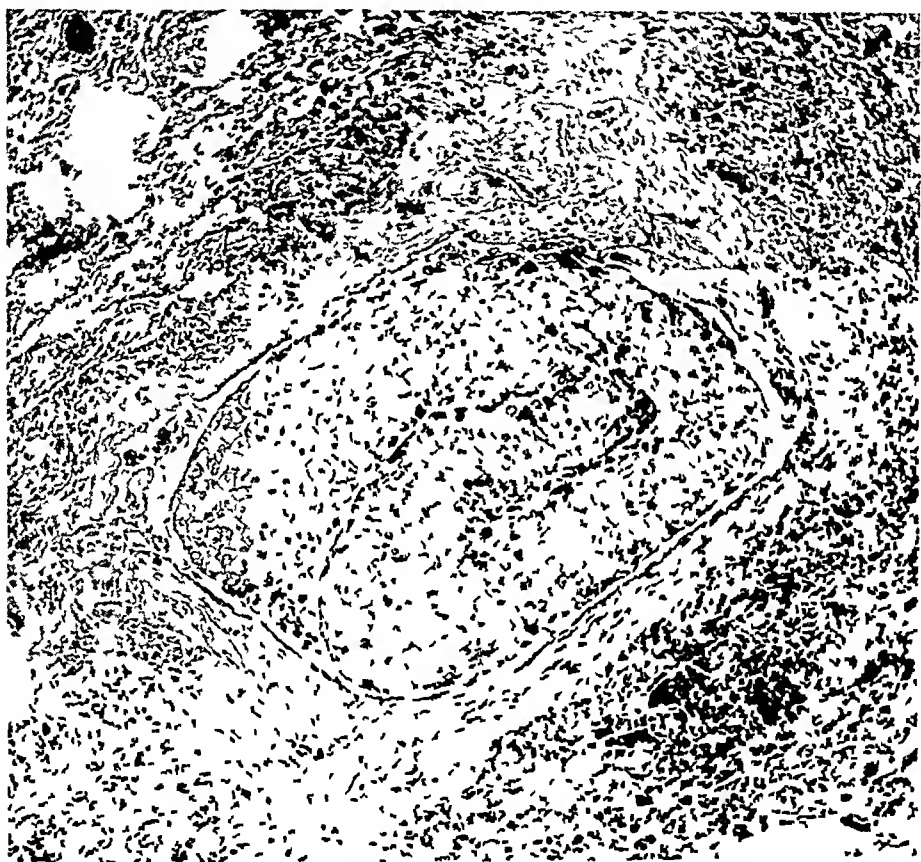


Fig. 4—A section through a pulmonary vessel thrombosed by neoplastic cells in bronchiogenic cancer. Tumor cells are also seen in the wall of the blood vessel. Methylene blue-eosin, $\times 80$.

hematogenous transmission to the brain of a "pus embolus" analogous to the transmission of a carcinomatous "cell embolus."

MATERIAL AND TECHNIC

The material consisted of eleven brains and ten specimens removed at operative exploration. In four instances, the surgical material only was available for study, while in the other, both material obtained at operation and tissues obtained at necropsy were studied.

Tissues were fixed in a 10 per cent solution of formaldehyde and also in Zenker's fluid

Paraffin sections were stained with hematoxylin and eosin, with methylene blue and eosin and also with phosphotungstic acid and hematoxylin. Frozen sections were studied with Bielschowsky's silver nitrate method, with Penfield's¹⁵ combination method for microglia and oligodendroglia and also with the gold chloride sublimate method as modified for formaldehyde-fixed tissue by Globus¹⁶

REPORT OF CASES

CASE 1—Sudden onset with numbness and tingling of left arm Jacksonian attacks and loss of memory Cerebral exploration with removal of tumor Microscopic diagnosis carcinoma, probably metastatic from the lung



Fig 5—A section through an organized neoplastic thrombus in a pulmonary vessel. Tumor cells are also present in the vasa vasorum. The insert shows the canaliculi of a thrombosed pulmonary vessel, lined by tumor cells. Eosin-methylene blue, $\times 80$

History—On March 18, 1927, a Canadian physician, aged 67, was referred for observation by Dr John Stewart of Halifax, Nova Scotia. The symptoms of the illness began suddenly three months before admission when the patient felt his

¹⁵ Penfield, W. A Method of Staining Oligodendroglia and Microglia (Combined Method), *Am J Path* **4** 153, 1928

¹⁶ Globus, J. H. The Cajal and Hortega Glia Staining Method. A New Step in the Preparation of Formaldehyde-Fixed Material, *Arch Neurol & Psychiat* **18** 263 (Aug) 1927

left arm become numb and tingle. One week later, twitching of the muscles of the left hand, arm, leg and left side of the face occurred and lasted for several minutes. These attacks recurred repeatedly. Soon he began to drag his left leg and had severe headaches. This was followed by loss of memory and by periods of disorientation. There were no general pressure symptoms.



Fig 6—Invasion of wall of a cerebral vessel and thrombosis by metastatic cells from a bronchiogenic carcinoma. Tumor cells are seen in the vasa vasorum. There also is necrosis of the vessel wall. Hematoxylin and eosin, $\times 110$.

Physical Examination—There was a weakness of the left side, a weakness of the lower part of the left side of the face, astereognosis of the left hand and a failure of memory. Although there was no choking of the optic disks on admission, there was a choking of over 2 diopters before the operation. An intracranial tumor was suspected and an exploration performed.

Course of Illness—On March 30, 1927, Dr. Cushing removed a nodule from the upper portion of the right postcentral convolution. The histologic sections showed a carcinoma, probably of pulmonary origin. The roentgen films of the lung were interpreted as showing no tumor. The patient was discharged improved on April 8, 1927. He continued to improve and regained much of his former activity for about the next eighteen months, and then in September, 1928, he began to fail again. In the next six months there was a gradual failure, until death occurred on April 7, 1929, almost two years from the date of his operation and about thirty months from the onset of his illness. The brain was removed

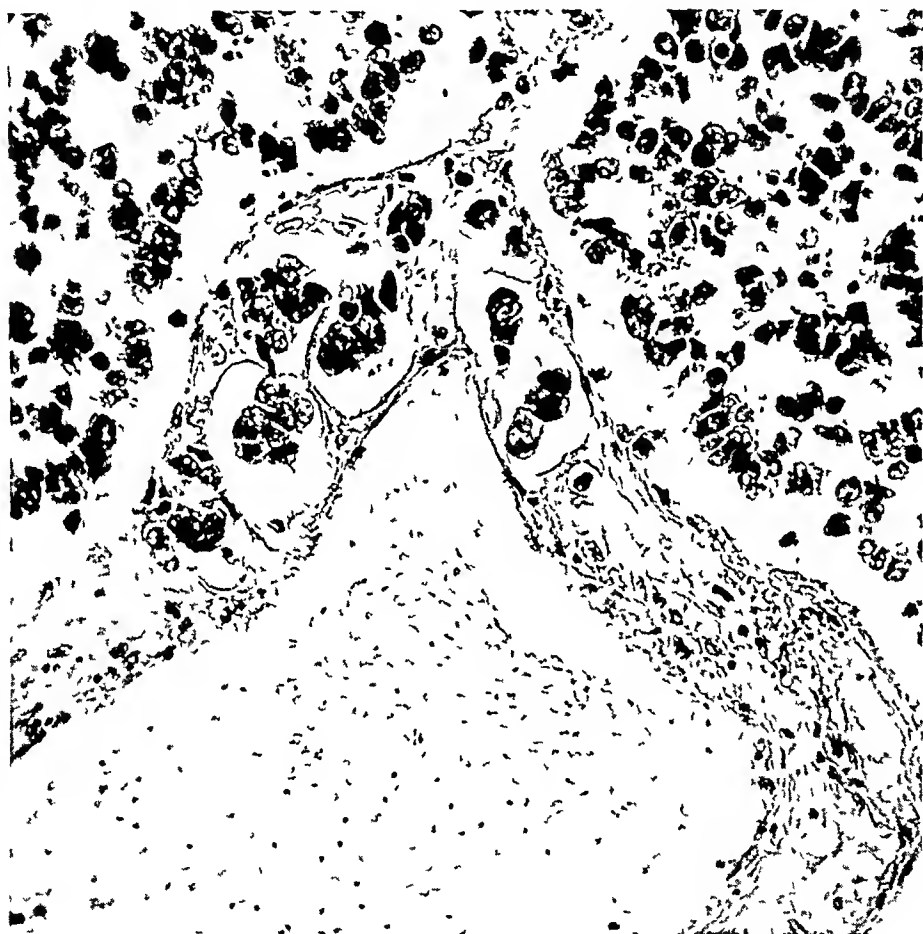


Fig 7—A section of a cerebral blood vessel showing neoplastic cells from a bronchiogenic carcinoma in the vasa vasorum. Hematoxylin and eosin, $\times 300$

by Dr. R. P. Smith of Halifax, Nova Scotia, and sent to this department for examination.

Brain—A series of thin coronal sections demonstrated three large typical metastases (fig. 8). Two were symmetrically located in the posterior part of the frontal lobes just below the corpus callosum, each measuring 1.5 cm. in diameter. At the site of the previous operation was a large metastasis 5 cm. in diameter. All these nodules were well demarcated and appeared enucleable. Their centers were opaque and necrotic, while the borders consisted of pinkish-red translucent, tumor tissue.

The meninges did not appear unusual.

Microscopic Examination—The sections of the specimen taken at operation showed a malignant epithelial tumor resembling other examples of metastasis from cancer of the lungs. The cells were columnar, forming acini with papillary projections, lined by neoplastic cells. The sections through the recurrent metastatic nodule at the site of the operation showed a dense gliosis in the adjoining brain substance. There was also a marked response on the part of the macrophages (fig 9).

Comment—The death of this patient occurred as the result of the multiple metastases to the brain with the consequent high degree



Fig 8 (case 1)—Metastases to the brain from a primary carcinoma of the lung. The insert shows a section through the old operative site to show the recurrence of a metastasis two and one-half years after the operation. The center of each nodule is necrotic. The brain was distorted in transportation.

of intracranial pressure. One of the interesting features of this case is the fact that there were no known symptoms of a pulmonary lesion during the relatively long survival period.

The roentgenogram of the skull was interpreted as showing some porosity of the cranium over the suspected site of tumor, and from these observations a meningioma was believed to be present. The sudden onset of symptoms suggested either a cerebral vascular lesion or a cerebral metastasis. The further course of the illness, with the

gradually increasing papilledema, made it certain that an intracranial tumor was present. There was no evidence of a primary tumor elsewhere. The first roentgenograms of the thorax were interpreted as showing no definite evidence of a tumor, although there were shadows at the hilum of the right lung. At a reexamination of the films it was suggested, however, that the roentgenologic aspect of the chest was compatible with a primary carcinoma of the lungs.

CASE 2—Onset with general weakness, cramps in legs, unsteadiness of feet, headaches, left spastic hemiplegia and extreme choking of optic disks. Cerebral

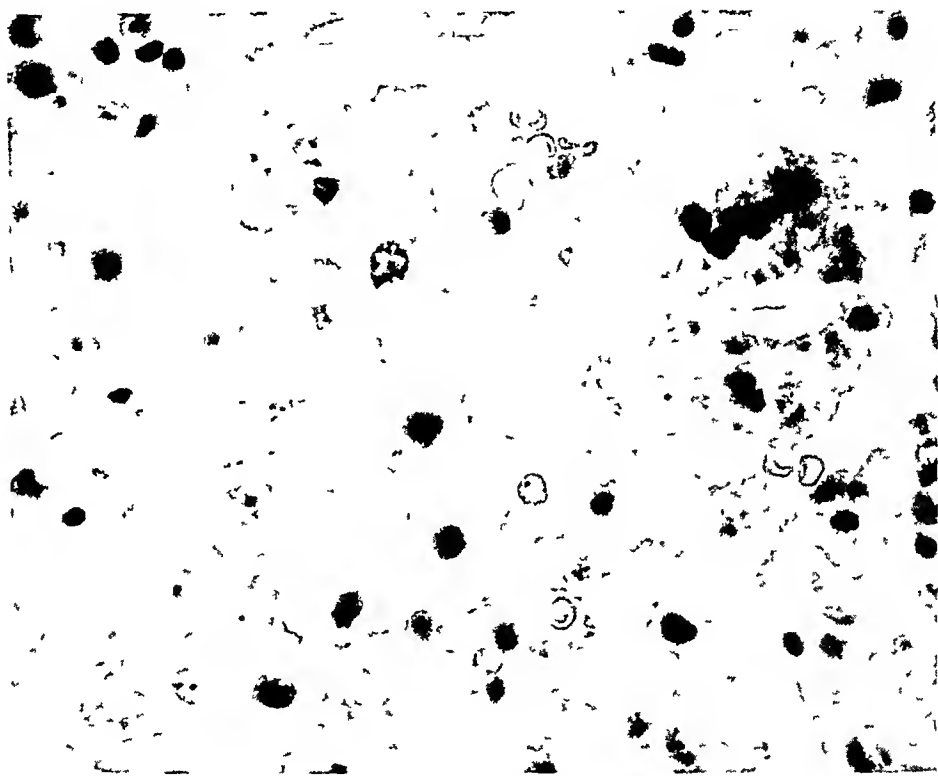


Fig 9 (case 1) —Macrophage reaction at the periphery of a metastatic nodule. Eosin-methylene blue, $\times 600$

tumor suspect. Operation with removal of tumor. Death. Postmortem finding of primary carcinoma of bronchus with metastases to the brain.

History—On April 22, 1927, Joseph D., aged 44, was referred by Dr. R. Wood of New Bedford, Mass. The present illness began four months before admission with general weakness, cramps in the legs and vague pains throughout the body. A diagnosis of rheumatism was made, and a tonsillectomy was performed. The patient had a severe postoperative hemorrhage. Shortly after the operation, he became unsteady on his feet, had severe headaches and was incontinent of urine.

Physical Examination—The patient was disoriented, speechless and incapacitated by a left spastic hemiplegia. Both optic disks were swollen with scar tissue and hemorrhages, denoting that the papilledema had been present for some time.

Course of Illness—It was the impression that a tumor was present in the right precentral region. Two days after admission, he had a slight hemoptysis, cough-

ing up blood-streaked mucus. The results of an examination of the lungs were considered as normal.

On April 28, 1927, a right cerebral exploration was made by Dr. Cushing and what was considered in the gross and by immediate microscopic examination as a meningioma was removed from the right precentral area. The patient died twenty-four hours after the operation.

Necropsy—The body was well nourished. There was a primary carcinoma of the bronchus to the right upper lobe with almost complete occlusion of this bronchus and contraction of the pulmonary artery to the right upper lobe. Metastases were found in adjacent bronchial lymph nodes, in the right kidney and in the brain.

Brain. The entire superior longitudinal sinus was occluded by a recent thrombus. A number of coronal sections showed an unusual edema of the entire brain and but one degenerated metastatic nodule in the tip of the left frontal lobe.

Microscopic Description—*Lungs*. The cells were cuboidal and arranged in alveoli with frequent tufting of the cells, so that they projected into the lumen from three to four cells in height. The blood vessels and the lymph vessels were invaded by the tumor. One large lymph node was replaced by tumor, and a section of a nerve showed that it, too, was invaded by tumor.

Brain and Meninges. There was an infected thrombus filling the superior longitudinal sinus. There was much necrosis of the brain elsewhere than near the metastases. The metastases were necrotic, and living cells were seen best at the periphery, where they formed collars about all the vessels. The response of the fibrous astrocytes, glomerulodendrosis of some of these cells, the changing of microglia into phagocytic cells and the swelling of the oligodendroglia were followed in the selectively stained sections.

Comment—Here is another example of the difficulty of clinical diagnosis of this type of lesion in the central nervous system.

The choking of the optic disks apparently occurred early in the course of the disease, as the scar tissue formation indicated. The hemoptysis two days before the operation was not investigated and no roentgen examination of the chest was made. At the operation, Dr. Cushing remarked about the pronounced cerebral edema and the presence of an unusual tumor embedded in the cerebrum. At the immediate investigation of the operative specimen, it was thought that it was a meningioma. The finding of a bronchiogenic carcinoma of the right upper lobe was a complete surprise.

The clinical history of this patient bears a close resemblance to that of the patient in case 1. In each case, the interval from the onset of symptoms to operation was short, and in each instance a tumor was removed from the right motor area. In case 1, however, there was late choking of the optic disks and little cerebral edema, in this case, there was advanced choking of the optic disks and great edema. Possibly because of that, this patient died soon following the operation, while the patient in case 1 lived for over two years after the cerebral exploration.

CASE 3—*Sudden onset with headaches, unconsciousness, convulsions, early signs of intracranial pressure Dysarthria Drowsiness Cerebral tumor suspected Right occipital exploration with finding of two enucleable tumor nodules Pathologic diagnosis metastatic cancer Death two months later Necropsy*

History—On Sept 30, 1927, George J., a Lithuanian, a railroad yard worker, aged 49, was referred by Dr E L Hunt of Worcester, Mass., with a diagnosis of tumor of the brain. Two and one-half years before admission, he was operated on for a gastric ulcer. The present illness began suddenly three months before admission with a severe headache. He went to bed, but had a generalized convulsion four hours later. On regaining consciousness, he had a most severe frontal and occipital headache. Within the next three days, he had had three similar attacks. Dizziness began shortly afterward and continued until the admission. In the month before admission, he developed tinnitus in the right ear, dysarthria, dimness of vision and projectile vomiting.

Physical Examination—The patient was well nourished. There was a swelling of both optic disks of from 3 to 4 diopters. A slight weakness of the left side of the face was noted during the periods of examination. The patient was drowsy. The roentgenogram of the skull was interpreted as showing a tumor in the right hemisphere, for areas of calcification were shown posterior to and above the pineal gland.

Course of Illness—Localizing signs of a tumor were absent, therefore, in order to save vision, a right subtemporal decompression was made. The patient was somewhat relieved by this procedure and was discharged on Oct 24, 1927. Soon the severe headaches recurred, and he returned to the hospital on Nov 10, 1927.

On Nov 18, 1927, a right occipital exploration was made by Dr Horrax, and encapsulated, hard tumors which resembled metastatic lesions were removed. The immediate examination of this tissue showed it to be a metastatic adenocarcinoma the primary origin of which was undetermined. On the day before discharge, Dec 3, 1927, the only roentgenogram of the lungs made was interpreted as showing a small area of consolidation in the upper right middle lobe, "probably an incompletely resolved pneumonia."

There was temporary improvement after the operation, but soon a recurrence of the previous symptoms caused a gradual decline, with death occurring on April 29, 1928, about nine months from the onset of the symptoms of an intracranial lesion. A complete necropsy was made at the Worcester City Hospital, and the organs were forwarded here for examination.

Necropsy—The body was well nourished. An adenocarcinoma of a bronchus with metastases to the suprarenal glands, kidneys and brain was found. The tumor originated in the bronchus to the right upper lobe and had metastasized to the adjacent bronchial lymph nodes. In the kidneys and suprarenal glands there were single, encapsulated, firm, metastatic nodules.

Description of Specimens—The two metastatic nodules removed at operation from the right parietal and temporal lobes were reddish-gray and enucleable, and measured 3 and 1 cm in diameter, respectively.

The brain was edematous, with flattened convolutions. Innumerable metastases were scattered in every portion of the brain. At least 100 nodules ranging from a few millimeters to 2 cm in diameter were seen in the thin coronal sections of the entire brain. All these nodules were firm and grayish-red and showed little necrosis in the gross.

Lungs The primary tumor was made up of columnar cells arranged in alveolar form. There was a tremendous increase in the connective tissue in which collections of tumor cells appeared to be isolated. The only invasive portion of the tumor was beneath the bronchus, and here the cartilage and entire wall were invaded by tumor cells. Frequently, tumor cells were found in the lumen of blood vessels.

Brain The tumor cells in each of the metastatic nodules appeared much more malignant than the cells of the primary tumor. They were columnar and cuboidal and each had a deep, irregular, hyperchromatic nucleus. They were often piled up in layers from two to four cells deep. Frequently, groups of large, single cells with enormous irregular, deep blue-staining nuclei invaded the brain. As in previous cases there was some response on the part of the fibrillary astrocytes and the microglia.

Comment—The sudden onset with headache and convulsions ushered in the clinical symptoms of an intracranial lesion. There were no symptoms or clinical observations of the bronchiogenic tumor. As in many cases in which metastatic cerebral lesions are present, the localizing signs were so indefinite as to warrant, at first, only a subtemporal decompression. The general pressure symptoms with a high degree of papilledema were noticeable early. They were associated with the extreme edema of the brain rather than with a hydrocephalus.

The results of the necropsy need but little comment. The small primary tumor which had invaded many lymphatics and adjacent small blood vessels was typical of carcinoma of the bronchus. The metastases duplicated the histologic structure of the primary tumor.

It is noteworthy that the results of a roentgenologic examination performed about five months before the patient's death were interpreted as showing an unresolved pneumonic process and not a new growth.

CASE 4—Sudden onset of cerebral symptoms in 1919 with weakness and paralysis of right side. Early choking of optic disks. Subtemporal decompression (elsewhere). In 1920, at a cerebral exploration a necrotic, infiltrating tumor was removed. Pathologic diagnosis: carcinoma. Death at home. No necropsy.

History—On May 31, 1920, James H., an American farmer, aged 41, was referred by Dr. J. Higgenbotham of Sunken Gardens, Va., with a diagnosis of tumor of the brain. The patient had always been well, except for influenza about six months before the onset of his present illness. A chronic nonproductive cough followed, and a diagnosis of pulmonary tuberculosis was made, but never verified. The onset of the cerebral symptoms occurred suddenly four months before admission. At that time he fell off his porch, and when picked up was found to have a weakness of the right foot. Soon the entire right side was weak, and the signs of increased intracranial pressure were apparent in dimness of vision, headaches and vomiting. A subtemporal decompression was made, but it was followed by only temporary relief.

Physical Examination—The patient was emaciated. There was a paralysis of the entire right side, and also a motor and sensory aphasia. The optic disks were swollen.

Course of Illness—On June 9, 1920, Dr. Cushing made a left osteoplastic exploration and partially removed a cystic tumor from the left hemisphere. The

cyst content was mucoid, and a direct smear revealed cocci and bacilli, although a culture of the same material showed no growth. The microscopic sections of the tumor were interpreted as showing a papillary adenocarcinoma, probably of the choroid plexus.

On June 26, 1920, shortly before discharge, a roentgen examination of the chest was made. The chest was asymmetrical with the mediastinum displaced to the left side and an increase in the shadows of the left hilum and posterior mediastinum at the level of the bifurcation of the trachea, interpreted as a mediastinal tumor.

The patient returned home, and died on Sept. 8, 1920, about seven months from the onset of the cerebral symptoms. Necropsy was not allowed.

Description of Specimen Obtained at Operation—A collapsed cystic structure with masses of grayish-white tumor attached represented the specimen. The mucoid material adhered to the thin-walled cystic portion.

Microscopic Examination—The tumor cells were all of the tall columnar type arranged in small cysts and glandlike structures into which there were papillary projections of the tumor. Mitoses were commonly found and when present the cells were distorted and appeared polygonal in shape. The cells did not tend to invade the brain either directly or along the walls of the blood vessels. Moderate gliosis was present in the adjacent cerebral tissue.

Comment—Although the tumor in this case was an adenocarcinoma, no one ever thought that its primary source might well be in the lungs. The roentgenologic examination of the chest was performed because pulmonary tuberculosis was suspected, and the finding of a new growth characteristic of a bronchiogenic tumor was a surprise. The decompression effect of the cerebral exploration relieved the patient's symptoms for a few months.

CASE 5—Onset in 1922, with right hemiplegia and aphasia. Cerebral tumor suspected. Exploration, with removal of malignant epithelial tumor from left motor area, primary source unknown. Recurrence of symptoms six months later. Second exploration. Complete recovery. In 1928, discovery by roentgen examination of a carcinoma of the lungs. Death. Necropsy not allowed.

History—On Nov. 14, 1928, Henry S., a Russian Jew, aged 70, was admitted to the medical service for observation. He had previously been in the surgical service three separate times, following December, 1922, for two intracranial operations and for the repair of a hernia. The onset of the illness in question occurred about July, 1922, with the gradual development of paralysis of the right arm and leg and apraxia¹⁷. On examination, the optic disks showed a choking of 2 diopters, and there was a spastic hemiplegia on the right. A diagnosis of tumor of the left motor area was made, and an enucleable tumor, weighing 85 Gm., was readily removed from that region on Dec. 22, 1922.

The patient was discharged three weeks later free from symptoms.

Six months later there was a recurrence of the symptoms, and at a second operation a tumor weighing 45 Gm. was enucleated from the same site as the first tumor. Three weeks later, the patient was discharged, entirely free from symptoms.

¹⁷ This aspect of the case was investigated by Bailey, P. A Contribution to the Study of Aphasia and Apraxia, Arch Neurol & Psychiat **11** 501 (May) 1924.

He was reexamined in December, 1925, and found to be normal, and indeed he lived a normal life until Sept 4, 1928, then a right femoral hernia became incarcerated. While the patient was in the hospital for repair of the hernia, a study was made to find out the source of the metastatic cerebral lesion removed six years before. The gastro-intestinal tract, the genito-urinary tract, the prostate and the skin were ruled out by study. Signs of localized impaired resonance and abnormal breath sounds in the left upper lobe were found. Stereoroentgenograms of the lungs showed a soft shadow in the left upper lobe corresponding to the pathologic area found in the clinic.

Following this admission, the patient coughed up blood-streaked sputum which showed no tubercle bacilli or abnormal cells.

Within a short time after his discharge, the patient began to lose weight, began to have a productive cough and had severe pain in the intercostal regions and the right arm. He was then readmitted to the hospital, to the medical service, where clinical evidence of diffuse involvement of the lungs was confirmed by the roentgen examinations. Apparently there were also metastases to many of the bones.

He died on Nov 22, 1928, about seven years after the onset of the cerebral symptoms. Necropsy was not permitted.

Microscopic Examination—Brain. Sections of the separate metastatic nodules removed at operation in 1923 were available for study. Previous to the clinical demonstration in 1928 of the evidence of a carcinoma of the lung, various diagnoses were made from these slides. Areas suggesting either a chordoma or a metastatic "hypernephroma" were described.

After having studied a large number of sections of metastatic lesions of the brain, especially of metastases from tumors of the lungs, we are convinced that the cells of this tumor were epithelial in origin and in all probability came from a primary tumor of the lung. There was an abundance of necrosis, but where the tumor cells were better preserved they grouped themselves in alveolar arrangement with multiple papillary projections into the lumen. The cells were high cuboidal, were without cilia and had deep black, irregular nuclei. There was little reaction to be seen in the small portion of the attached brain tissue. When the tumor cells were necrotic, they appeared huge and rounded or polygonal with small eccentric nuclei and an abundance of cytoplasm.

Comment—The patient was studied thoroughly by the members of the surgical and medical staffs of the hospital. It appeared beyond any reasonable doubt that the secondary epithelial growth removed from the brain in 1922 had metastasized from the lungs, at that time, the pulmonary lesion was probably in the early stage of its development. The patient survived more than six years after the removal of the metastatic nodule. This case again is of interest in connection with the advisability of intracranial exploration, which we shall take up in the general comment. It also shows that bronchiogenic cancer, as probably do most cancers, grows slowly, particularly in persons of advanced age.

CASE 6—*Gradual onset with headaches, loss of strength and loss of vision. Weakness of the right side of the face. Osteoplastic exploration with removal of large cystic tumor. Histologic diagnosis metastatic epithelial tumor. Recurrence of symptoms followed by a second operation twenty months later with removal of a large cyst. Recovery. Sudden death from pulmonary embolus two weeks after operation.*

History—On April 6, 1925, Mrs G, a Jewish housewife aged 46 was admitted to the medical service of this hospital with the complaint of headaches. The onset of the illness five months before admission was sudden with severe headaches. Soon there was a gradual loss of vision and of strength.

Physical Examination—There was evidence of a slight loss of weight. Weakness of the right side of the face and bilateral choking of the optic disks were the only other positive observations.

Course of Illness—The patient was considered as having a tumor of the brain and was transferred to the surgical service. A ventriculogram demonstrated a block of the left foramen of Monro and a multiventric tumor in the left occipital lobe.

On April 25, 1925, Dr Cushing performed a left occipital exploration and removed a cystic tumor. The fluid in the cyst was mucoid and yellow and contained cholesterol crystals, fat and macrophages.

The microscopic sections showed a carcinoma probably of bronchiogenic origin.

The chest was then examined by the roentgen rays and revealed a tumor in the hilum of the left lung.

The patient made an uneventful recovery and was discharged improved.

The patient was seen at intervals during the next two years. One year after the operation, there was distinct clinical evidence of a cerebral embolus the effects of which gradually wore off. At times there was some evidence of pleurisy on the left side and occasional hoarseness.

On Feb 18, 1928, symptoms of intracranial pressure recurred and the patient was readmitted to the hospital. Roentgen examination of the lungs made then showed in the left hilum a shadow which was somewhat increased in size as compared with that seen at the first examination. A careful search for a neoplasm elsewhere in the body revealed none.

A second exploratory operation was then performed on Feb 28, 1928 and a cystic tumor was removed from the same location as the previous tumor (fig 10).

The patient was making a normal recovery when death occurred suddenly on March 6, 1928, about three years from the onset of the cerebral symptoms. Necropsy was not permitted.

Description of Specimens—The first specimen removed in 1925 from the left occipital lobe consisted of a multilocular cystic mass about 5 cm in diameter. It contained over 30 cc of dirty orange fluid, the examination of which disclosed macrophages, cell debris and many cholesterol crystals. The wall was thin and local thickenings of grayish-white tissue represented mural nodules of tumor.

The second specimen (fig 10), removed in 1928 from the same location as the first cyst just described consisted of a large oval cyst, measuring after fixation 9 by 6 cm and containing more than 75 cc of a material similar to that found in the first specimen. This large cyst had a thin, transparent wall and contained one large mural mass of grayish-white tissue about 3 cm in diameter and 2 cm in height. This tissue was partially necrotic and resembled both the tissue from an early primary tumor of a bronchus and other metastases to the brain in this group.

Sections of the metastasis removed in 1925 and in 1928 were available for study. There was an abundance of mucoid material and crystals. The tumor cells in both specimens were low cuboidal cells arranged in thick strands or alveoli. There were relatively few mitoses. The nuclei were less hyperchromatic and the cells appeared smaller in the specimen removed in 1925 as compared with the last.

specimen In the first specimen there would be some doubt as to the origin of the primary tumor However, in the second specimen the cells resembled those observed in several other cases of this series in which the presence of primary tumor of the lung was confirmed by necropsy

Comment—When the histologic examination of the cerebral tumor revealed a carcinoma the attention of the staff was directed to the visceral organs in order to locate the primary source of the disease In addition to the roentgenologic examination of the gastro-intestinal tract and of the genito-urinary organs a roentgenogram was taken of the chest It revealed the presence of the primary new growth

The records of the Peter Bent Brigham Hospital show that from 1913, the year of the foundation of the hospital, to 1925, a certain



Fig 10 (case 6) —A cystic metastatic tumor from a primary tumor of the lung, removed at a second operation performed two years after the first operation

number of patients with histories similar to those recorded here were under observation in the clinics After the nature of the cerebral lesion was disclosed, investigation was usually directed to every visceral organ except the lungs, and the patients were discharged with the diagnosis of carcinoma, metastatic to the brain, primary source unknown Since it became apparent that the brain is the common site of metastases from primary tumors of the lungs, a correct diagnosis of this condition has been made in nine instances during the last three years

The patient was examined by roentgen rays on six occasions within two and a half years These examinations showed an extremely slow advance of the primary intrathoracic lesion

The intracranial exploration with the removal of tumor by Dr Cushing two times in about thirty months is noteworthy. Indeed, but for the unfortunate accident of a pulmonary embolus, the patient's life would possibly have been prolonged for years, as in case 5.

CASE 7—Sudden onset of symptoms with twitching of muscles of face and aphasia. Cerebral tumor suspect. Cerebral exploration without result. Increase of symptoms, right hemiplegia. Reexploration with finding of tumor. Microscopic diagnosis: metastatic epithelial tumor. Death. No necropsy.

History—On June 25, 1925, James G., a native American, aged 56, was admitted for the second time, with a diagnosis of tumor of the brain. The patient was well until March 8, 1925, then he suddenly felt twitching of the muscles of the right side of the face with difficulty in forming words. Four days later he had three similar attacks. On March 26, 1925, a cerebral exploration was made, but a tumor was not located. After several deep roentgen treatments the patient was discharged. However, there was a rapid increase in his symptoms with paralysis of the right arm and leg and difficulty in speaking.

Physical Examination—On this second admission, the patient was semiconscious. There was a right sided hemiplegia. The optic disks were swollen.

Course of Illness—A preoperative diagnosis of glioma in the left parietal lobe was made, and at an exploration on June 27, 1925, Dr Cushing removed the great part of a partly degenerated tumor. The lesion in the gross resembled a glioblastoma multiforme. Some time later, a diagnosis of malignant epithelial tumor, probably of pulmonary origin, was made. On July 21, 1925, a roentgen examination of the chest showed a large, rounded mass in the left upper lobe, and the diagnosis of primary tumor of the lung was made. The patient made an uneventful recovery and was discharged on July 28, 1925. He improved for a time and then became worse. He died at home on Oct 26, 1925, about seven months after the onset of the cerebral symptoms. Necropsy was not made.

Microscopic Examination of Surgical Specimen—The metastatic tumor was composed of cuboidal cells with large deep-staining, irregular nuclei. The cells were arranged in one or many layers to form glandlike structures. There was considerable necrosis. In the adjacent brain tissue was an evident gliosis with phagocytosis.

Comment—The relief from symptoms in this case, as in case 2, was of a few months' duration only. We therefore believed that although palliative, a cerebral exploration was indicated.

CASE 8—Onset of illness with cough followed later by headache and loss of weight. Sudden onset of intracranial pressure. Roentgenologic demonstration of carcinoma of lung. Palliative suboccipital decompression with early fatality.

History—On Dec 20, 1928, Owen O'D., a native American, aged 48, was referred to the medical service for observation. For one year before admission, the patient had a cough productive of thick, yellow sputum. Two months before the admission, he came to the outpatient service complaining of attacks of severe headache which had been present for about five months. The patient also stated that he had lost about 35 pounds (14 Kg.) in weight in the preceding year.

The patient was admitted to the hospital. A lumbar puncture was done on Dec 1, 1928. The cerebrospinal fluid pressure and the results of various tests were within normal limits. He was discharged, but the increase in the severity of

his headaches and the onset of unsteadiness in gait and dimness of vision caused him to seek readmission to the medical service on Dec 13, 1928. A gradual development of choked disks was found, and the patient was transferred to the surgical service on Dec 20, 1928.

Physical Examination—Despite the stated loss of weight, the patient was well nourished. Both optic disks showed about 3 diopters of swelling. Involvement of the right fifth, seventh and eighth cranial nerves was found. The gait was ataxic. There was no nystagmus.

Course of Illness—A roentgen examination of the chest was difficult of interpretation and the diagnosis lay between tuberculosis of the left upper lobe and



Fig 11 (case 8)—Metastases in the cerebral hemispheres and in the basal ganglion (indicated by arrows)

tumor. A second roentgen examination of the chest, eight days after the first one, unquestionably showed the shadow of a tumor in the hilum of the left lung.

In the hope of aiding the patient by getting rid of the pressure symptoms, Dr. Cushing made a suboccipital exploration on Jan 2, 1929, and removed one of the degenerated metastatic nodules from the left hemisphere of the cerebellum. Death occurred on Jan 6, 1929. Complete necropsy was made.

Necropsy—Postmortem examination showed primary carcinoma of the bronchus of the upper lobe of the left lung with metastases to the adjacent lymph nodes, pancreas, right kidney and multiple metastases to the brain, also acute necrotizing bronchopneumonia.

Multiple metastases in the brain were located as follows: in the right frontal lobe, in the basal ganglia on the left side (fig 11), in the gray matter of the parietal lobe, in both hemispheres of the cerebellum and in the vermis. All

these nodules were grayish-red and sharply marked off grossly and showed little necrosis. The meninges did not show gross abnormalities.

Microscopic Description—Lungs. The tumor cells were low cuboidal cells with small, hyperchromatic nuclei and little cytoplasm. They resembled the basal cells of the bronchial mucosa. The tumor invaded the walls of the blood vessel, and their lumina, as well as the lymphatics. They grew in nests in the alveoli and did not appear to line the walls of the alveoli. A great part of the remainder of the lungs was the seat of an acute inflammatory process.

Brain. The tumor appeared to be the most invasive of all of the metastatic pulmonary tumors. There were numerous polymorphonuclear leukocytes about and in the metastases, so that real microscopic abscesses resulted. Small nests of cells invaded blood vessel walls and lined the intima causing a thrombus formation in which blood and tumor elements were mixed. Similar nests of cells invaded the brain and leptomeninges. A tremendous number of phagocytes and a fibrillary astrocyte response, as well as changes in the microglia and acute swelling of the oligodendroglia were seen.

Comment—Although the presence of a pulmonary tumor in this case was disclosed before the cerebral exploration was performed decompression was decided on to alleviate the patient's suffering. The rapid fatal issue was due to a necrotizing pneumonia and also to the fact that the brain was heavily invaded by the malignant tumor.

CASE 9—Sudden onset with aphasia and right spastic hemiplegia. Early pressure symptoms. Cerebral tumor on left side suspected. Osteoplastic exploration with negative results. Death three weeks after operation. Necropsy.

History—On Dec. 31, 1928, Carrie S., an American housewife, aged 58, was referred by Dr. Fred M. Lowe of West Newton, Mass., with a diagnosis of tumor of the brain. The illness began suddenly on Oct. 5, 1928, about three months before admission while the patient was working at home. She felt her right arm and leg become weak and numb and noticed also dimness of vision. Her husband was soon aware of his wife's inability to form words and speak intelligibly although she was able to understand. She was hospitalized. The increasing swelling of the optic disks suggested that an intracranial tumor was present.

Physical Examination—The patient was obese. Motor aphasia, anosmia, right hemiparesis and hemiparesthesia were present. There was a high degree of swelling of the optic disks measured at 5 diopters. The extra-ocular movements of the left eye were present.

Course of Illness—Because of the high grade of choked disk, a left osteoplastic exploration was made shortly after admission with the expectation of finding a glioblastoma multiforme. A tumor was not located, but the great edema of the brain forced the sacrifice of the bone flap. There was only a temporary improvement, and death occurred on Jan. 25, 1929, about three and one-half months from the onset of the symptoms. Complete necropsy was permitted.

Necropsy—Postmortem examination revealed primary carcinoma of the middle branch of the right bronchus with metastases to the peribronchial lymph nodes, left lung, brain, liver, left kidney and left suprarenal gland.

The body was well nourished.

The carcinoma took origin in the bronchial mucosa. The greater part of the middle lobe was replaced by partly broken down new growth which on being sectioned resembled closely a blood vessel tumor. In addition, the artery to the

right lower lobe was completely occluded by a recent thrombus. The right common carotid artery was also occluded by a recent thrombus situated at a point where sclerotic changes of the vessel wall were most marked. The left lung contained one metastatic nodule.

In the brain, the entire left hemisphere was edematous. Just posterior to the site of operation in the parietal lobe there was a single metastatic nodule 3.5 cm in diameter, which extended from just beneath the cortex. Many sections of the brain failed to show any further metastases.

Microscopic Examination—Lungs. Necrosis and hemorrhage in the new growth were present to such an extent that there was little well preserved tumor. An inflammatory reaction of the walls of the large blood vessels, resulting in thrombosis, was a common observation and this may account for the extensive necrosis.

The tumor cells were columnar, and were arranged as alveoli with papillary projections into the lumen.

Brain. The tumor cells in the one metastatic nodule were actively invading the adjacent brain from the meninges and from the periphery of the metastasis. More necrosis was seen about this single large metastasis than in any other material studied. There were multiple small collections of necrotic material and polymorphonuclear leukocytes resembling abscesses both at the periphery and among the tumor cells. In the paraffin sections were seen tremendous numbers of phagocytic cells in the adjacent brain. Frozen sections of the same material stained for microglia showed a most remarkable response on the part of these cells, demonstrating changes of these cells into actively phagocytic cells.

There was more clasmatodendrosis of the responding fibrillary astrocytes than was seen in other cases of this series. The oligodendroglia cells from all over the brain showed swelling of the cytoplasm.

The tumor cells were arranged as alveoli and were usually high columnar. However, many groups of cells were piled up to resemble transitional epithelium.

Comment—The sudden onset with hemiplegia and aphasia suggested, at first, a cerebral vascular accident. With the finding of choked disks and increasing intracranial pressure, a diagnosis of cerebral tumor was made. The short history and the changes suggested the presence of the most invasive and rapidly growing of the gliomas, the glioblastoma multiforme. A tumor was not disclosed at operation, although the edema of the brain was such that the tissue was almost fluid.

The finding at necropsy of a primary carcinoma of the bronchus to the right middle lobe was unexpected. When the brain was sectioned, the tremendous edema and the single, localized and apparently enucleable metastatic nodule were found just posterior to the exploratory cerebral incision.

Roentgen examinations of the lungs were not made nor was an examination of the cerebrospinal fluid made during the course of the illness.

CASE 10—Occipital headaches followed by right hemiplegia and severe mental symptoms. Development of choked disks. Cerebral tumor of the left side sus-

pected Operation with finding of tumor in left motor area Death Necropsy Finding of primary carcinoma of bronchus

History—On Nov 25, 1927, Serafin G, a Spanish seaman, aged 67, was referred by the Boston Psychopathic Hospital with the diagnosis of tumor of the brain. The illness began two months before admission with weakness of the right leg and severe occipital headaches. Two weeks later, spastic paralysis of the right leg and then of the right arm developed. There was no history of symptoms of increased intracranial pressure. One month before admission, the patient was referred from a local hospital to the Psychopathic Hospital because of his mental symptoms. With the development of choking of both optic disks, he was referred to the surgical service of this clinic as suspected of having a cerebral tumor.

Physical Examination—The patient was uncooperative, aphasic and difficult to examine. Both optic disks were swollen to about 3 diopters. A spastic paralysis of the right arm and leg with a positive sign of Babinski and ankle clonus were present. The results of the various laboratory tests were reported as normal. The roentgen examination of the skull showed no localizing signs of a tumor.

Course of Illness—The preoperative diagnosis was difficult to arrive at. However, in view of the age and the short history of symptoms, a glioblastoma multiforme of the left motor area was considered as the most possible lesion. A left bone flap was made, and a nodule of tumor was easily enucleated from the motor area. An immediate examination suggested a metastatic adenocarcinoma. Portable roentgen ray films were made and interpreted as showing a large, rounded, soft tissue shadow in the outer portion of the right hilum. As the left side of the diaphragm was held high, it was thought that a primary tumor of the stomach was present with metastases to the lung and cerebrum. Evidence of an extensive respiratory infection began after the operation, and the patient died on Dec 8, 1927, about two and a half months from the onset of the symptoms. Complete necropsy was made.

Necropsy—Postmortem examination revealed a primary carcinoma of the bronchus of the right lung with multiple metastases to the brain, liver, suprarenal glands and right kidney, and extensive bronchopneumonia.

The body was well nourished.

The primary tumor involved the lower part of the upper lobe, the entire middle lobe and the upper part of the lower lobe of the right lung. The middle and lower bronchi were patent, but the upper bronchus was completely occluded, 1.5 cm from its origin, by the carcinoma. The sections of the lung showed a solid grayish-white tumor invading the adjacent lung tissue.

Brain Five large metastatic nodules were found in the left cerebral hemisphere, in the cerebellum and in the pons (figs 12 and 13). One nodule in the cerebellum so compressed the fourth ventricle that the ventricular system was dilated. The nodules were grayish-red with little necrosis. They were round, appeared to be perfectly demarcated and indeed could be readily chucked out of the brain (fig 12). The edema of the left hemisphere was remarkable in comparison with the relatively normal right hemisphere, in which no nodules were found.

Microscopic Examination—Lungs The sections through the primary tumor showed the invasive, rapidly growing, well preserved epithelial cells arranged, according to location, as glandlike structures or in small clumps. The entire wall of the primary bronchus was invaded, and the lining epithelium was replaced by tumor. Elsewhere in the lungs were edema, infarction and evidence of an acute

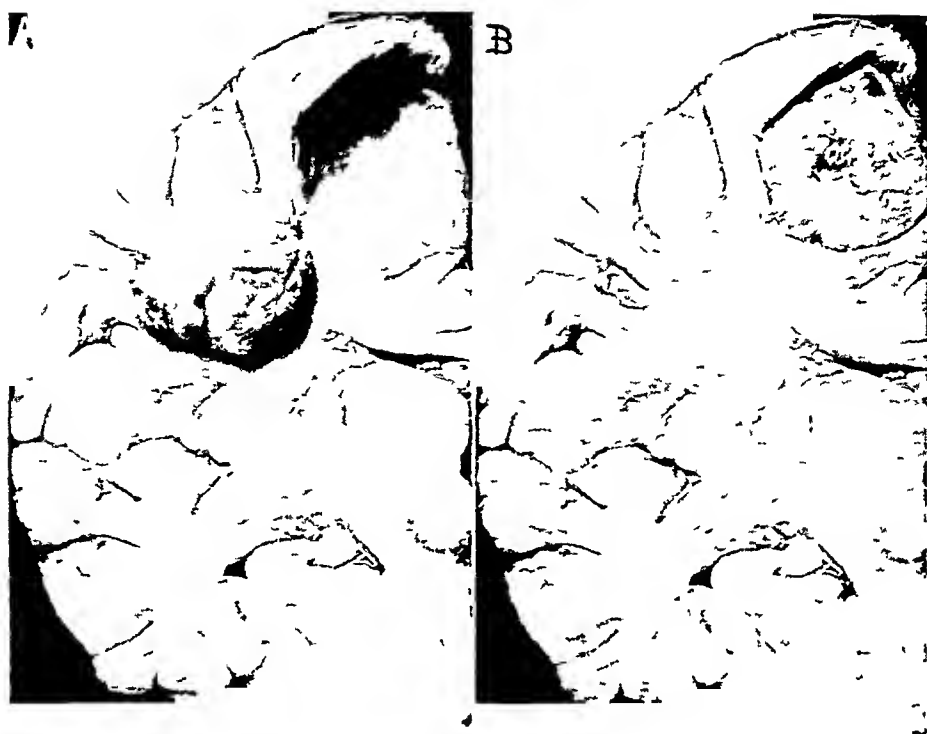


Fig 12 (case 10) —An enucleable solitary metastatic nodule in the cerebrum (*A*) removed from its bed and (*B*) in place



Fig 13 (case 10) —Metastases in the cerebellum from a bronchiogenic carcinoma.

inflammatory process. Separate from the tumor and in an area of normal lung tissue was an early stage of metaplasia of the lining epithelium of a bronchiole.

Many small blood vessels and lymph vessels were filled with tumor emboli. The walls of some vessels were invaded by individual tumor cells.

Brain. There were available for study the immediately fixed operative specimen and the necropsy material, fixed six hours post mortem.

The cells of the metastasis were similar in arrangement and type to those of the primary tumor. The cytoplasm was plentiful, and the cells were either

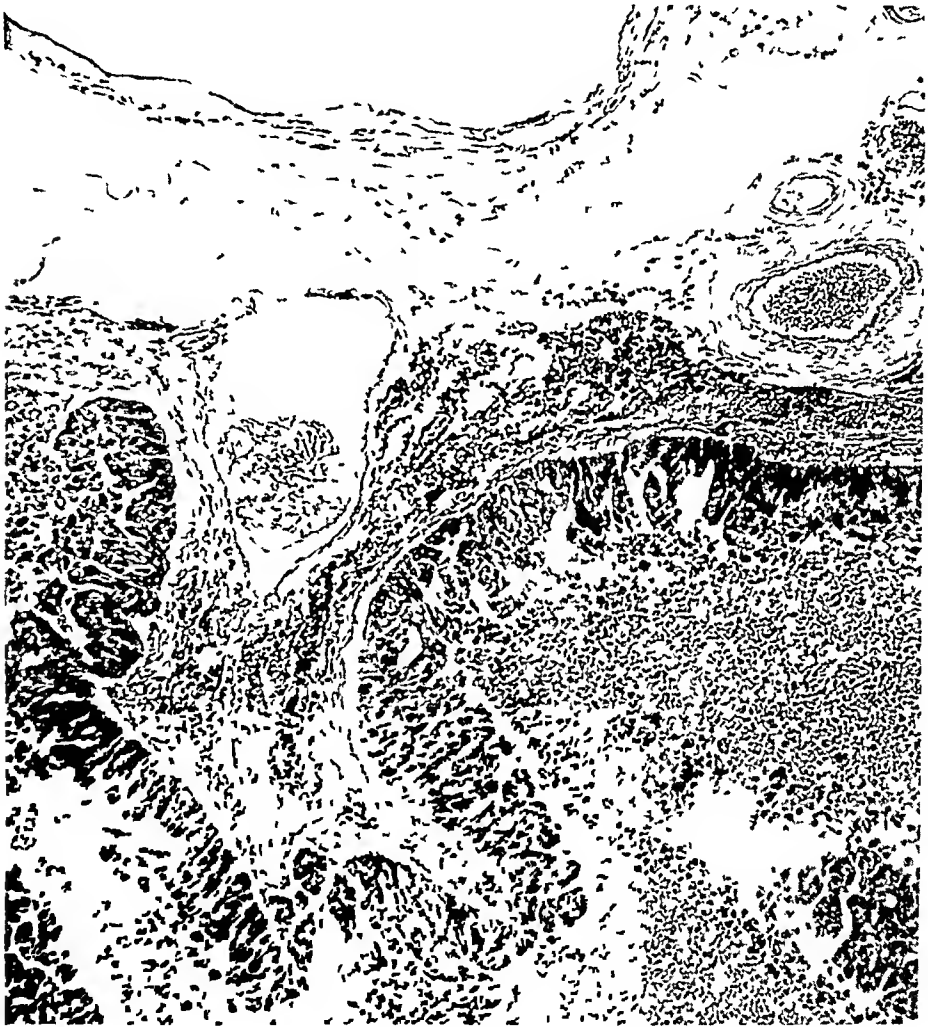


Fig 14—A section through the tumor nodule shown in figure 12. The cortex is completely replaced by tumor cells, which line the under surface of the pia mater. There is no invasion of the subarachnoid space. Hematoxylin and eosin, $\times 80$.

columnar or high cuboidal and often occurred in many layers like the arrangement of transitional epithelium. Mitoses were abundant. The tumor invaded the brain along the periphery of small blood vessels, and by direct invasion of the tissue with groups of tumor cells (fig 14). With the routine paraffin sections stained with eosin-methylene blue and phosphotungstic acid one could study many aspects of the injury to the brain and the brain's response.

For a short distance about the tumor, the brain tissue was necrotic, the nerve cells were disintegrated and the myelin sheaths were broken up, and one saw only the large phagocytic cells and the cell bodies and processes of both degenerated and active fibrous astrocytes. There was also seen a proliferation of the fibrous astrocytes for some distance away. Except for the phagocytosis and response of the astrocytes, no other part of an inflammatory response was to be seen.

The frozen sections stained specifically for astrocytes and for oligodendroglia and microglia demonstrated special changes in these elements. There were hyperplasia and hypertrophy of many of the fibrous astrocytes which "streamed" toward the metastasis (fig 15). The degenerative change of these cells, clasmato-dendrosis, was especially well shown.

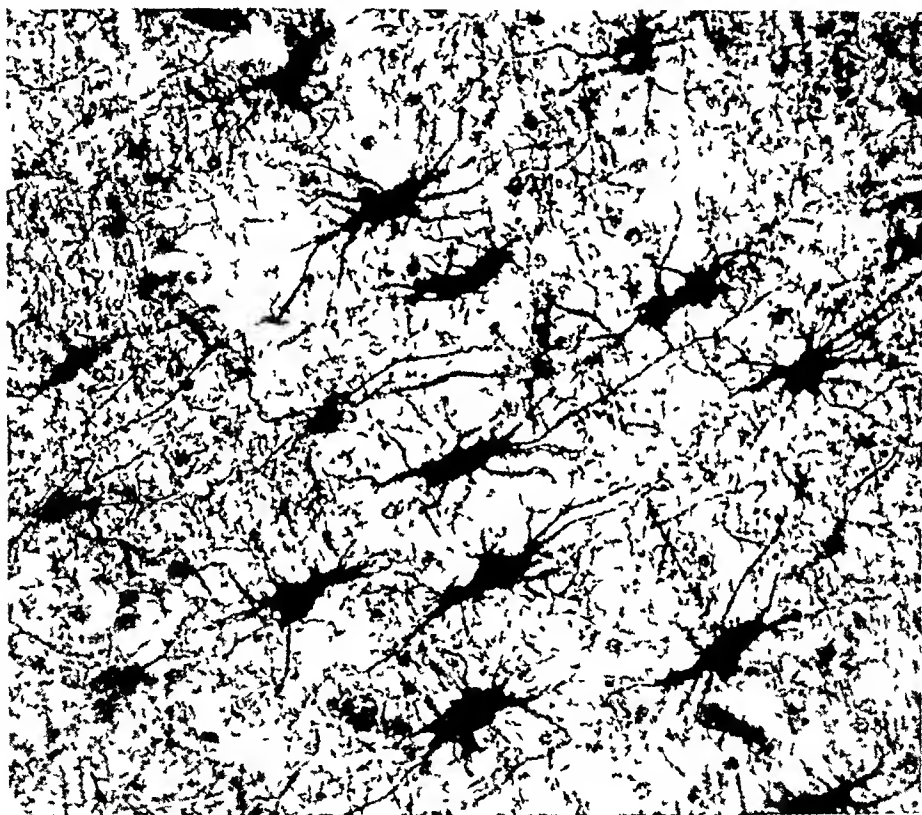


Fig 15—The reaction of fibrillary astrocytes in the vicinity of a cerebral metastasis from a primary cancer of the lung. There are a proliferation and an increase in size of these cells. The arrangement of these cells gives the impression that they are streaming toward the lesion. Gold chloride sublimate (Globus modification), $\times 320$.

The oligodendroglia both in the specimen obtained at operation and in those obtained at necropsy were in the swollen stage, but there was no evidence of any activity on their part in the repair of the injury.

Just as Hortega and Penfield demonstrated the transformation of microglia into phagocytic cells about experimental wounds and tumors of the brain so one could follow these changes in the brain tissue about the metastases. A short distance from the edge of the tumor tissue, the microglia increased in numbers and soon changed their form to that of the type of phagocytic cell known as gitterzellen.

Comment—The outstanding symptoms in this case were those of mental changes, leading to hospitalization in three separate hospitals before the changes in the eyegrounds suggesting an intracranial tumor were recognized at the Psychopathic Hospital. The aphasia and inability to obtain a concise history were the great stumbling blocks in the interpretation of the lesions. The choking of the disks occurred early after the onset of symptoms.

It is interesting to note that in the presence of a relatively small primary tumor there was an extensive invasion of the blood vessels by neoplastic cells and also multiple nodules in the brain.

In this case, as in cases 1 and 3, the roentgenologic examination of the lungs gave a negative result.

CASE 11—Onset insidious with tiredness, headache, nausea and vomiting. Subtemporal decompression. Glioma of right frontal lobe suspected. Osteoplastic exploration on right side with removal of tumor. Early fatality. Necropsy with finding of primary carcinoma of the lungs and multiple metastases to brain.

History—On Dec 15, 1913 Miss A. W., an American nurse, aged 48 was referred by Dr. J. T. Mitchell of Middleton, Conn. with a diagnosis of tumor of the brain. Previous to the onset of the illness, the patient had been treated for asthma for several years. The exact onset of the present illness was difficult to determine. The patient felt tired in February, 1913, but continued at work. Seven months later, in September, 1913 she had the first of a series of frontal and suboccipital headaches accompanied by nausea and vomiting. Various treatments were outlined and given, but with no relief. Finally a diagnosis of cerebral tumor was made.

Physical Examination—The patient was well developed and well nourished. There was a high degree of choking of the optic disks. The tongue protruded to the right. Aphasia was noted. Ataxia of the extremities and exaggeration of the deep reflexes were conspicuous.

Course of Illness—A definite localization of the tumor could not be made. A subtemporal decompression was made on Dec 21, 1913. In the next several weeks, the patient became worse, and finally epileptiform attacks suggested a cerebral lesion on the right side, and an osteoplastic exploration was made by Dr. Cushing on Jan 13, 1914. An unusually edematous brain was found and a 'gelatinous,' stringy, mucoid tumor about 3 cm. in diameter was removed from the right frontal lobe. There was an early postoperative fatality.

Necropsy—The body was well nourished. A primary carcinoma of the bronchus to the right lower lobe with metastases to the brain was present.

Brain—The brain was edematous and protruded through the operative defect in the skull. There were innumerable small and large cystic cavities measuring from 0.5 to 3 cm. in diameter and filled with a gelatinous, stringy material. These were found everywhere in the brain, being evenly distributed and suggesting an arterial spread.

Microscopic Examination—A number of sections through the specimen removed at operation and of specimens taken from the brain at necropsy were studied. There was extensive necrosis in the center of each of the metastases and at the periphery, in the brain substance. The tumor cells were columnar and polygonal, with abundant mitoses, and were arranged to form small cysts or

glands Tumor cells were found in the walls of blood vessels and in their lumen, as emboli and thrombi, and also as cuffs about the adventitia The leptomeninges over the cerebrum were lined in one portion by tumor cells

Comment—This case belongs to the early series in which the patients came to the hospital for treatment There was an early fatal issue, and the necropsy revealed a bronchiogenic tumor

The finding of a primary carcinoma of the lungs was unexpected In retrospect, the recommending physician recognized that the patient's heart was displaced and that the area of cardiac dullness was increased, suggesting some abnormality of the midthoracic region The presence of the pulmonary tumor probably accounts for these physical abnormalities The insidious onset of the cerebral symptoms was more in keeping with a primary tumor of the brain than with a metastatic lesion As is often the case with metastatic lesions to the brain, the clinical picture was a confusing one and the localization most difficult

The multiple metastases suggested an arterial spread of the neoplasm

CASE 12—Onset sudden with paralysis of the left side of the face Disorientation Dysarthria Early choking of optic disks Regarded as alcoholic psychosis Death without operation Necropsy with finding of carcinoma of bronchus and multiple metastases to various organs, brain and leptomeninges

History—On Oct 23, 1921, George S., an English chef, aged 55, was admitted to the surgical service for observation The onset of the illness occurred suddenly on Sept 20, 1921, with a paralysis of the left side of the face In addition, the patient was temporarily disoriented Following the onset dysarthria, mental changes and the symptoms of increased intracranial pressure developed

Physical Examination—The patient was disoriented, restless and emaciated A left facial paralysis was noted There was a slight choking of the optic disks The results of the examinations of the blood, urine and spinal fluid were negative The blood pressure was elevated, with a systolic pressure of 160 mm and a diastolic pressure of 80 mm

Course of Illness—A diagnosis of alcoholic psychosis was made, as it was known that the patient was a heavy user of alcohol Signs of consolidation of the left lung were evident shortly after admission, and death occurred sixteen days later

Necropsy—Postmortem examination showed a primary carcinoma of the bronchus to the lower lobe of the lung with metastases to the brain, suprarenal glands, liver, hilar lymph nodes, right lung and upper lobe of the left lung

The body was well nourished The left pleural cavity contained about 30 cc of blood-tinged fluid A firm, grayish-white tumor, about 7 cm in diameter, surrounded and invaded the bronchus to the lower lobe of the left lung The tumor projected into the lumen of this bronchus so as almost completely to occlude it The tumor extended in fine strands from its periphery into the adjacent pulmonary tissue There were innumerable small, nodular metastases, never larger than 0.5 cm in diameter, scattered throughout the rest of the tissue, but especially beneath the visceral pleura

Brain Multiple metastases were found in the brain in the leptomeninges of the brain and spinal cord and along the dorsal root ganglions

The largest nodule in the brain was located in the left occipital lobe. It measured 5 by 3 cm. Other smaller nodules were found along the sylvian fissure in the floor of the fourth ventricle in the caudate nuclei and in innumerable other areas. All these nodules were grayish pink and appeared to be sharply marked off from the surrounding tissue.

Local thickening of grayish-white metastatic nodules was seen in the leptomeninges in the cervical and thoracic region about all the dorsal root ganglions.

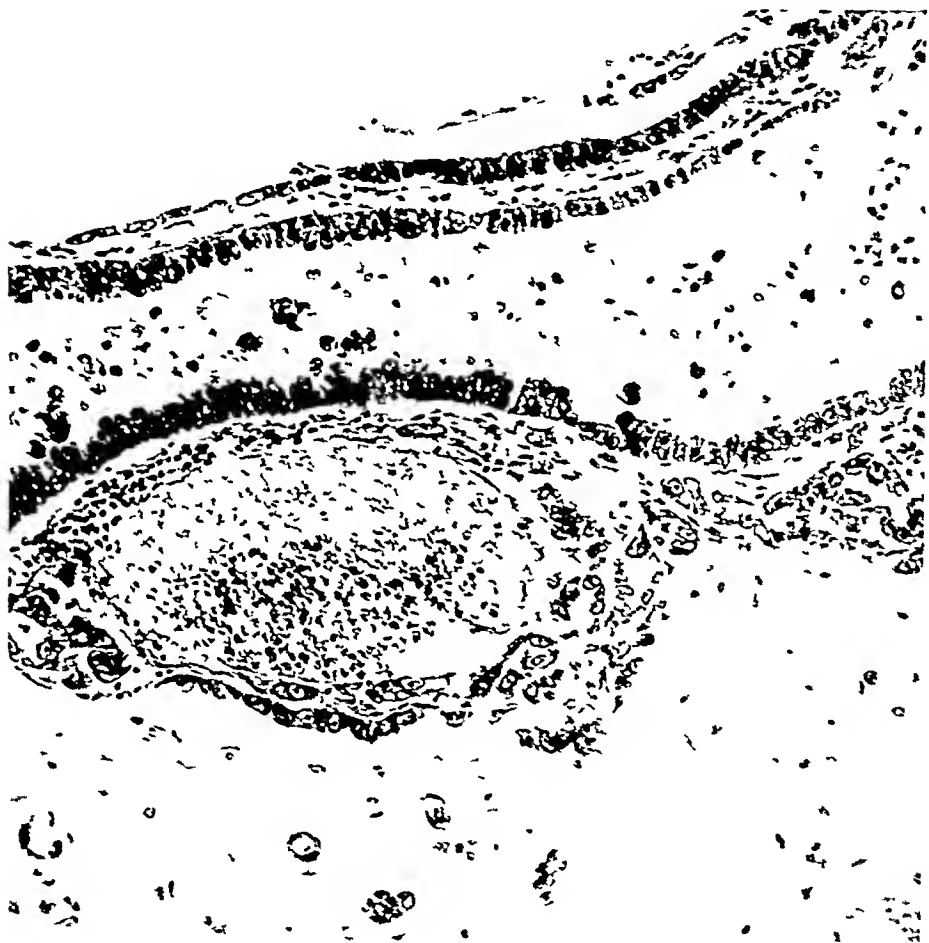


Fig 16—The leptomeninges are lined by neoplastic cells from a primary carcinoma of the lungs (localized meningitis carcinomatosa). Tumor cells are seen in the subarachnoid space and in the cerebral cortex. Eosin-methylene blue, $\times 150$.

Microscopic Examination—Lungs There was much necrosis of the tumor. A great number of blood and lymph vessels had their walls infiltrated and their lumen partially or completely occluded by tumor cells. Throughout the lungs were multiple scattered metastases which appeared to have been transported by the blood stream.

Brain and Meninges Both sharply demarcated and infiltrating tumor masses involved the brain, the leptomeninges of the brain and of the spinal cord and even some of the spinal nerves. The cells grew along the surface of the leptomeninges and replaced the usual lining (fig 16).

It is of interest that while ordinarily the tumor cells were columnar, when they lined the subarachnoid spaces and extended out into the dorsal root ganglions they took on a cuboidal aspect. No invasion of the spinal cord was seen.

Comment—The sudden onset of cerebral symptoms with mental changes in this patient, who was an addict to alcohol, suggested an alcoholic psychosis to the examiners. The absence of complaints and of any history referable to the respiratory tract in the presence of such an advanced lesion in the lungs is noteworthy. In the central nervous system, the tumor invaded the cerebral substance, the leptomeninges of the hemispheres and likewise those of the cord, which is unique.

CASE 13—*Onset of illness with pain in lumbar region and inability to walk. Exploratory laparotomy with finding of myomas of uterus. Postoperative wound infection and consolidation of base of left lung. Death. Autopsy with finding of primary carcinoma of bronchus to left lower lobe with metastases to brain, pelvic bones, liver, suprarenal glands, brain and to a meningioma of brain.*

History—On March 13, 1923, Minnie C., a Jewish housewife, aged 57, was referred by Dr. C. E. Williams of Roxbury, Mass., for observation. The illness began five months before admission with a dull pain in the lower part of the back and inability to walk. About two months later, the first of a series of persistent night sweats began. Within a short time before admission, the patient expectorated a small amount of blood.

Physical Examination—The patient was well nourished. There was rigidity in the lower part of the abdomen with tenderness in the left lower quadrant. Several nodules were felt in the left side of the body of the uterus. The examination of the thorax and lungs showed no abnormality. A neurologic examination likewise showed no disease. The cerebrospinal fluid was normal. The roentgen examination of the chest showed a wedge-shaped area of consolidation in the left lower lobe, the nature of which was not explained.

Course of Illness—After a thorough study, no lesions were demonstrated in the genito-urinary, gastro-intestinal, biliary or nervous systems. A pelvic exploration was made, and a hysterectomy was performed because of the myomas. The operative wound became infected, and the patient showed all the symptoms of increasing involvement of the lower lobe of the left lung. Death occurred two and a half months after admission to the hospital. A complete postmortem examination was made.

Autopsy—Postmortem examination showed a primary carcinoma of the bronchus to the lower lobe of the left lung with metastases to the lung, pelvic bones, liver, suprarenal glands, brain and the meningioma.

Lungs—A short distance from its origin, the bronchus to the lower lobe of the left lung was partially occluded by a carcinoma which extended from this bronchus for about 3 cm. into the lung tissue in all directions. The mucosa of this bronchus was eroded as the tumor projected into the lumen and for some distance to each side. The peribronchial lymph nodes were replaced by tumor.

Brain—The convolutions were flattened. One metastatic nodule, 1.5 cm. in diameter, was found in the left posterior parietal region. A meningioma, 2 cm. in diameter, was found over the right frontal lobe. This tumor caused erosion of the overlying cranium. A section of this hard tumor revealed areas of grayish-white tissue mixed with the dense, calcareous meningioma.

Microscopic Examination—Lungs The cells of the primary tumor were cylindric and were arranged as alveolar structures. The walls of blood vessels and their lumina contained nests and clumps of tumor cells.

Brain The section through the metastatic nodule showed it to be of the same structure and cell type as the primary tumor. The invasion of the meningioma represented a most unusual and rare instance of a benign new growth being invaded by a malignant tumor.

Comment—This case belonged to the 'old' series of cases in which the patients came to this hospital before a study of this condition was inaugurated by one of us and attention called to the frequent occurrence of this disease. Although the patient gave a history of hemoptysis and of night sweats, and although roentgen examinations pointed toward pathologic changes in the chest, no particular attention was paid to the thoracic organs. The patient then went through a pelvic operation, remaining in the hospital seventy-five days without the bronchiogenic tumor being recognized.

This patient also is of interest in that in addition to the bronchiogenic cancer she had a myoma of the uterus and a meningioma. The latter was infiltrated by the pulmonary cancer, which also had metastasized to the brain.¹⁸

CASE 14—*Sudden onset of cerebral symptoms with headache. Hemiplegia on the left. Cough for five years. Early fatality. Necropsy with finding of primary carcinoma of bronchus and metastases to the brain.*

History—K. L., a man, aged 45, was admitted to the Cambridge (Mass.) Hospital with the complaint of severe headache and pain in the back and neck. For five years before admission, the patient had had a cough. The onset of cerebral symptoms was sudden eight days before admission, with a severe, generalized and continuous headache.

Physical Examination—The patient was emaciated. There were signs of an active abnormal process over the apex of the left lung.

Course of Illness—There was a gradual development of a left hemiplegia, and the patient died seven days after admission and about fifteen days after the onset of the cerebral symptoms. A complete necropsy was performed.

Necropsy—Primary carcinoma of the bronchus to the upper lobe of the left lung was found, with metastases to the adjacent lymph nodes and brain.

Lungs The upper central division of the primary bronchus to the upper lobe of the left lung was the apparent seat of the primary carcinoma that invaded almost the entire upper lobe. The tumor apparently advanced eccentrically and uniformly from this one point of origin. The lymph nodes at the bifurcation of the trachea were massive from metastases.

Brain The meninges and blood vessels appeared normal grossly. After the brain was sectioned, five separate well preserved metastatic nodules, measuring from 1 to 4 cm in diameter, were found in the right frontal, parietal and occipital lobes and in the right cerebellar hemisphere.

¹⁸ Fried, B. M. Metastatic Inoculation of a Meningioma by Cancer Cells from a Bronchiogenic Carcinoma, *Am J Path.*, to be published.

Microscopic Examination—The primary tumor was made up of columnar cells arranged in alveolar form. The cells were not ciliated nor did they produce mucus. They appeared to grow along the walls of the alveoli. Many blood vessels were invaded and occluded by tumor.

The cells of the metastases to the brain were similar to those of the primary tumor. There was considerable necrosis of the tumor and also an extensive necrosis of the brain about the metastasis.

Comment—It is likely that the tumor of the left lung was of long standing, as the patient had a chronic cough for five years. The symptoms of metastases to the brain were of short duration, and the condition and extent of these metastases suggested that they were of recent origin and had occurred at about the same time. It is also of interest that all the metastases were on the right side of the brain, as in all the cases studied, the primary tumor had invaded the walls and lumen of many of the pulmonary vessels.

CASE 15—Onset with pain in right shoulder, weakness and loss of weight. Cough. Pulmonary tuberculosis suspected. Rapid course to fatality. Necropsy.

History—A man, aged 37, entered the Boston Sanatorium with the complaint of pain in the right shoulder and right knee. About three months before admission, the patient had had a sharp pain in the right shoulder, not related to injury. Soon diarrhea, weakness, loss of weight, an evening rise of temperature to 100 F and signs of involvement of the right lung caused the patient's hospitalization. There was a short history of cough with but little expectoration.

Physical Examination—The patient was emaciated. The chest was asymmetrical with a diminution of expansion on the right side. There were dulness and bronchial breathing over the entire right side of the chest and apical region of the left lung. The bones showed a chronic hypertrophic osteo-arthritis. The temperature increased to 100 F in the evening.

Course of Illness—During a three months' stay at the hospital the patient had severe pain along the spine, and during the last week he was delirious. Death occurred six months from the onset of the symptoms. The final diagnosis was that of chronic and acute pulmonary tuberculosis and chronic hypertrophic osteo-arthritis.

Necropsy—Postmortem examination disclosed primary carcinoma of the bronchus to the upper lobe of the right lung with metastases to adjacent lymph nodes, left lung, left kidney, brain and right femur and chronic hypertrophic osteo-arthritis.

Brain—Twelve large, softened metastases from 1 to 1.5 cm in diameter were found scattered in every part of the brain.

Microscopic Examination—The primary tumor replaced the pulmonary tissue, and in places the columnar cells growing in alveolar manner were replaced by squamous-like cells. Frequently, the walls of the blood vessels were invaded by the tumor cells, and the lumina occluded by a carcinomatous endophlebitis with resultant thrombus formation by both tumor and blood elements.

The metastases to the brain caused abundant necrosis and little reaction, as seen by the hematoxylin and eosin stained sections. The brain was invaded by tumor cells singly and in groups following along the blood vessels adjacent to the metastasis.

Summary of Cases

Case	Sex*	Age	Pulmonary Symptoms	Onset of Cerebral Symptoms	Optic Disks	Clinical Diagnosis	Cerebral Exploration and Result	Pathologic Diagnosis	Survival Following Operation
1	♂	67	None	Sudden with tingling of left arm and numbness	Showed no choking	Tumor of the brain	Removal of nodule from right postcentral convolution	Carcinoma metastatic from lung	Two years and four months
2	♂	41	None	Gradual with general weakness and pains throughout body	Showed advanced choking	Tumor of the brain	Removal of tumor from right precentral area	Bronchiogenic carcinoma metastatic to brain	(Postoperative fatality)
3	♂	49	None	Sudden with head aches, unconsciousness and convulsions	Choked	Tumor of the brain	Removal of tumor nodule	Bronchiogenic carcinoma widespread metastases	Seven months
4	♂	41	Nonproductive cough	Sudden with weakness in right foot and choked hemiplegia	Choked	Tumor of the brain	Removal of cystic mucoid tumor	Carcinoma metastatic from lung	Seven months
5	♂	70	None	Gradual development of paralysis of right arm and leg, apraxia	Choked	Tumor of the brain	Removal of tumor from left motor area	Carcinoma metastatic from lung	Seven years (1)
6	♀	46	None	Sudden with severe head aches	Choked	Tumor of the brain	Removal of tumor and of a large cyst	Carcinoma metastatic from lung	Two years and six months
7	♂	56	None	Sudden with twitching of facial muscles and paraphasia	Choked	Tumor of the brain	Removal of tumor	Carcinoma metastatic from lung	Five months
8	♂	48	Productive cough of one year's duration	Gradual with attacks of headache	Choked	Metastatic tumor of brain	Removal of metastatic tumor	Bronchiogenic carcinoma metastatic to brain	(Postoperative fatality)
9	♀	38	None	Sudden with numbness of right arm and dimness of vision	Showed advanced choking	Tumor of the brain	Tumor not found	Bronchiogenic carcinoma widespread metastases	(Postoperative fatality)
10	♂	67	None	Gradual with occipital headaches and hemiparesis	Choked	Tumor of the brain	Removal of tumor nodule	Bronchiogenic carcinoma widespread metastases	(Postoperative fatality)
11	♀	48	Asthma for several years	Gradual with frontal and suboccipital headaches	Showed advanced choking	Tumor of the brain	Removal of gelatinous tumor	Bronchiogenic carcinoma multiple cerebral metastases	(Postoperative fatality)
12	♂	56	None	Sudden with left facial paralysis and disorientation	Showed slight choking	Alcoholic psychosis	Brain not explored	Bronchiogenic carcinoma widespread metastases	(Death without operation)
13	♀	57	Hemoptysis on one occasion, night sweats	No cerebral symptoms	Not examined	Leiomyoma of uterus	Brain not explored	Bronchiogenic carcinoma widespread metastases	(Death without operation)
14	♂	45	Cough of five years' duration	Sudden with severe headaches	Not examined	Pulmonary tuberculosis	Brain not explored	Bronchiogenic carcinoma with metastases	(Death without operation)
15	♂	37	Cough	Sudden with delirium	Not examined	Pulmonary tuberculosis	Brain not explored	Bronchiogenic carcinoma widespread metastases	(Death without operation)

* In this table, ♂ indicates male, ♀, female

Comment—The bronchiogenic cancer in this case metastasized to the viscera, the bones and the brain. The history is lacking in details concerning the symptomatology and the duration of the cerebral involvement.

GENERAL COMMENT

Pathologic Observations—Lungs. In eleven cases the primary tumor was located near the hilum of the lung and originated in a primary bronchus or in one of its early divisions. The tumor led to a thickening of the bronchial wall for a short distance and extended out into the adjacent pulmonary tissue replacing it either diffusely or by fine projections. The lesion did not reveal a spread to the visceral pleura except in the instances in which the hilar portion of the right middle lobe was involved, and then the tumor extended into the adjacent portions of the upper and lower lobes.

The new growth presented a translucent surface studded with pigment and opaque necrotic tissue. One tumor of the middle lobe of the right lung along with the pulmonary tissue became so necrotic and infiltrated with blood that it resembled more a primary "blood vessel" tumor than a malignant epithelial neoplasm.

In most sections through these tumors there were seen small and large blood vessels occluded by recent or organized thrombi, and in one instance the tumor extended into a large vessel adjacent to the primary bronchus involved. Frequently, small infarcts of the lungs were seen. Occasionally, small nodular metastases to the same or to the opposite lung were noted, and in one instance the metastases were distributed as are the tubercles in miliary tuberculosis.

The adjacent tracheobronchial lymph nodes showed a varying degree of invasion by metastases but they were never greatly enlarged.

There were always changes in the lobe of the lung which was the site of the tumor as well as elsewhere in the pulmonary tissue. Such changes as atelectasis and compensatory emphysema, infarction and acute inflammatory processes were commonly found adjacent to the tumor as elsewhere.

The microscopic examination of these bronchiogenic tumors emphasized the variations in the types, the arrangements and the invasiveness of the malignant cells. Although there was always a variation in the size of the cells even in the same sections one type predominated in both the primary tumor and the intracranial metastases. The cells of this common type were columnar or cylindric and were arranged in a single layer or piled up to line a variable-sized alveolar-like structure into which there were often papillary projections of the cells. In the same tumor, cuboidal or large polygonal cells were also seen, singly, in groups or arranged in a glandlike structure. In two of the tumors cuboidal

cells predominated. Neither squamous cells nor the small undifferentiated cells described as "oat cells" were seen, and in no instance were the cells considered as having their origin from the mucous glands of the bronchi or from the "alveolar epithelium."

The degree of invasiveness varied in that in some there appeared little reaction on the part of the bronchus or pulmonary tissue, while in others the tumor cells appeared isolated in a dense, old scar tissue. In all the cases there was erosion of the bronchial epithelium with extension into the lumen and invasion of the bronchus. The cartilage, blood vessels and lymphatics were involved as much as the parenchyma.

The lesions in the blood vessels were most interesting. Tumor cells invaded the walls of vessels, of any caliber, projected into the lumen and frequently formed a new lining for the vessel. A thrombus composed of tumor cells and of blood elements often formed and became organized and canalized, and the canaliculi themselves then became lined with tumor cells (figs 3, 4, 5, 6 and 7).

Likewise, emboli made up of tumor cells were present in vessels of all calibers. Apparently, tumor emboli passed directly to the heart and from there into the general circulation, forming also metastases in distant visceral organs.

The atelectasis, hemorrhages, infarctions, emphysema and inflammatory processes seen in the gross were confirmed in all the microscopic sections.

Brain. Edema of the brain was noted at every intracranial operation and at necropsy. This was so conspicuous that the presence of the metastatic nodule never satisfied the operator that it alone could be the cause of such an edema, which often required the sacrifice of the bone flap.

Multiple thin coronal sections were made of each brain. The ventricles were never greatly dilated, and the choroid plexus always seemed normal in the gross. Likewise the cerebrospinal fluid showed no pathologic changes.

The metastases were firm, solid, enucleable masses, measuring up to 5 cm. in diameter; large enucleable, cystic masses as much as 9 cm. in diameter or necrotic, broken down lesions and as such resembled the most malignant and invasive of the gliomas, the glioblastoma multiforme. The solid metastases weighed as much as 50 Gm. The cystic metastases always had one or more mural nodules of typical carcinomatous tissue and had contents of more than 75 cc. of dirty, orange-colored mucoid material containing cholesterol crystals, phagocytic cells and debris. In one instance, bacteria were seen in smears of the cyst content but culture of this material showed no growth.

In two cases there were single, apparently enucleable masses, 5 cm in diameter. In three cases there were from six to twelve nodules of varying sizes located on the same side of the brain in each instance. Each of the remaining brains appeared to be literally riddled with about 100 separate masses, each of the same gross appearance. These appeared less enucleable and more invasive than the single metastases.

The location of the metastases is of interest in that in eight of eleven cases in which operation was performed, tumor was diagnosed and subsequently found in the motor areas. In two other instances, the lesion was correctly localized in the occipital region. In two patients, gross involvement of the leptomeninges of the cerebrum and spinal cord was seen in these thickened, grayish-white structures (fig 16).

The diffuseness and multiplicity of the metastases to the brain were convincing evidence of their being carried by the blood stream.

From the material removed at operation and at necropsy, certain aspects of the reaction of the brain to the tumor, hitherto undescribed, could be studied.

In general, the cells resembled those of the primary lesion, except that they were more frequently in mitosis. However, when these cells invaded the tissue of the brain singly or in small groups, they differed from the common cell type of the pulmonary tumors, in that they often were huge and rounded or polygonal and had large, irregular, hyperchromatic nuclei. The cell arrangement was similar to that in the primary tumor except for certain features. In one instance, a single layer of tumor cells lined the subarachnoid space of both the brain and the spinal cord just as the tumor cells lined the alveoli of the lungs (fig 16). Thick collars of tumor cells often surrounded the adventitia of blood vessels invading the brain alongside the vascular wall. The walls of large blood vessels at the periphery of some of the metastases were invaded by single cells or groups of tumor cells (figs 6 and 7).

The nerve fibers showed complete destruction in the close vicinity of the metastatic nodules. In areas remote from the lesion, the nerve fibers showed demyelination, swelling and fenestration. Changes in the ganglion cells were conspicuous in regressive and progressive changes in the cell body and in the nuclei, and also in the abnormal distribution of the Nissl substance.

In the paraffin sections, necrosis of the cerebral tissue and degeneration of the nerve cells and nerve fibers in the presence of some phagocytic cells and astrocytes was all that was visible of the reaction. But with the special stains referred to, the complexity of the reaction was conspicuous.

The activity that each individual cell displayed in the presence of the neoplastic invaders may be considered separately.

In general, the reaction in the brain closely resembled that described by Penfield¹⁹ as present in the vicinity of gliomas and also in experimental cerebral injury.

The microglia appeared normal at a distance of 1 cm from the edge of the metastasis. As the tumor nodule was approached, there was a rather abrupt transition to a mass of microglia which appeared to be wandering toward the necrotic tissue. Here the normal and also the transitional forms of this cell formed a dense black mass that thinned out as the actual necrotic zone was reached. Within a small area, all the changes from the normal microglia to the ameboid forms and the compound granular corpuscles were to be seen. The tumor masses themselves showed no penetration by the phagocytic and scavenger elements (figs 17 and 18).

Large phagocytic cells were likewise seen attached to and lying free about the adventitia of small blood vessels at the boundary of the tumor and the necrotic cerebral tissue. It is possible that some of these cells arose from the adventitia of the blood vessels (the adventitial cells of Marchand).

Similarly, the astrocytes responded to the malignant neoplastic elements. In the cerebral tissue close to the metastasis, clasmotodendrosis of these cells was conspicuous (fig 19). In the adjacent areas, a dense gliosis was present and then there was a stream of the astrocytes, all seeming to go in parallel rows toward the injury (fig 15).

There was no evidence that the oligodendroglia act as an element of phagocytosis or of repair²⁰. In every section of the material obtained at operation or at necropsy, varying degrees of swelling of the cells were conspicuous (fig 20). It may be said that no distinction could be made between the swollen cells found in the old, fixed necropsy material and the fresh tissue operation obtained at and those seen in apparently normal brains. Transformation of these cells into phagocytic cells, as noted by some writers²⁰ in experimental conditions, could not be identified.

In brief, then, all elements of the cerebral substance responded to the metastatic neoplastic invasion. The reaction was most outstanding, and, as stated, closely resembled that seen by Penfield and his associates in experimental studies on the cerebral reactions to wounds and to infectious invaders.

19 Penfield, W. Microglia and the Process of Phagocytosis in Gliomas, *Am J Path* **1** 77, 1925, The Mechanism of Cicatricial Contraction of the Brain, *Brain* **50** 429, 1927. Penfield, W., and Buckley, R. C. Punctures of Brain Factors Concerned in Gliosis and in Cicatricial Contraction, *Arch Neurol & Psychiat* **20** 1 (July) 1928.

20 Ferrara, Armando, and Davidoff, L. M. The Reaction of the Oligodendroglia to Injury of the Brain, *Arch Path* **6** 1030 (Dec) 1928.

In his recent monograph Lewin²¹ stated that the brain represents an "indifferent nonspecific nutrient medium" for heterologous neoplasms. In 1923, Murphy and Sturm²² found that transplantable mouse tumors grew actively when inoculated into the brains of rats, guinea-pigs and pigeons, whereas subcutaneous or intramuscular grafts in the same animals failed. It will be seen that in the material here presented the cerebral reaction toward metastases, which are in a sense a homologous

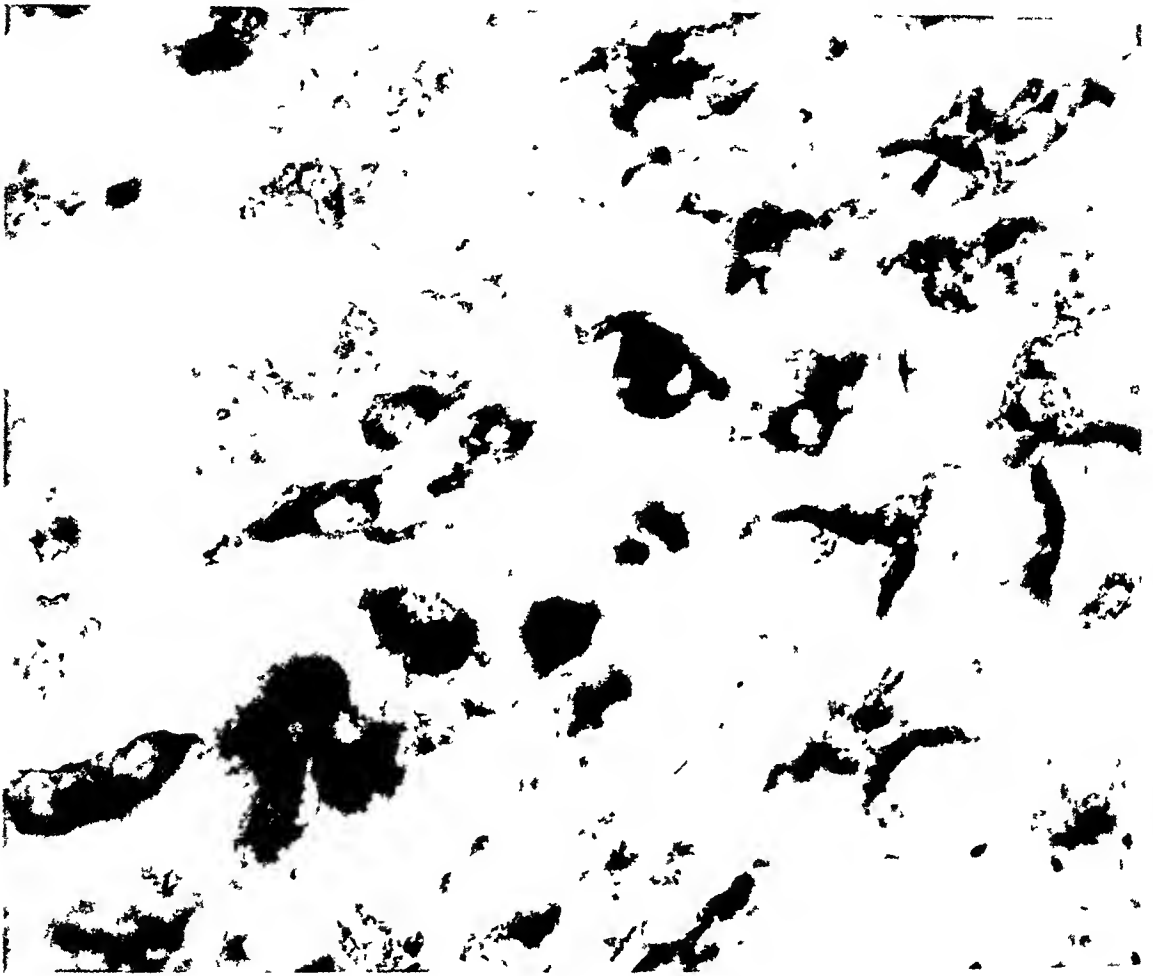


Fig 17—The reaction of the microglia to the metastases from a primary carcinoma of the lung. In the right segment of the picture the microglia show swollen processes. In the center, the processes are shortened and thickened, while in the left lower segment the cells are seen as compound granular corpuscles. Penfield's combined method for oligodendroglia and microglia, $\times 850$.

graft, is of such a magnitude that one can hardly accept the notion that the cerebral substance is an "indifferent nonspecific medium." Never-

21 Lewin, Carl. *Die Aetiologie der bösartigen Geschwülste*. Berlin: Julius Springer, 1928.

22 Murphy, J. B. and Sturm, E. Conditions Determining the Transplantability of Tissues in the Brain. *J. Exper. Med.* 38: 183, 1923.

theless, the malignant cells overcome this reaction and probably grow more rapidly in the brain than in the lungs

Clinical Observations—Onset of Symptoms In nine of the fifteen cases, the disease started suddenly and in six it began less abruptly. The patients of the first group could state accurately the circumstances, the date and often the hour of the onset of the first attack. In six of the nine patients the initial symptoms were those of involvement of

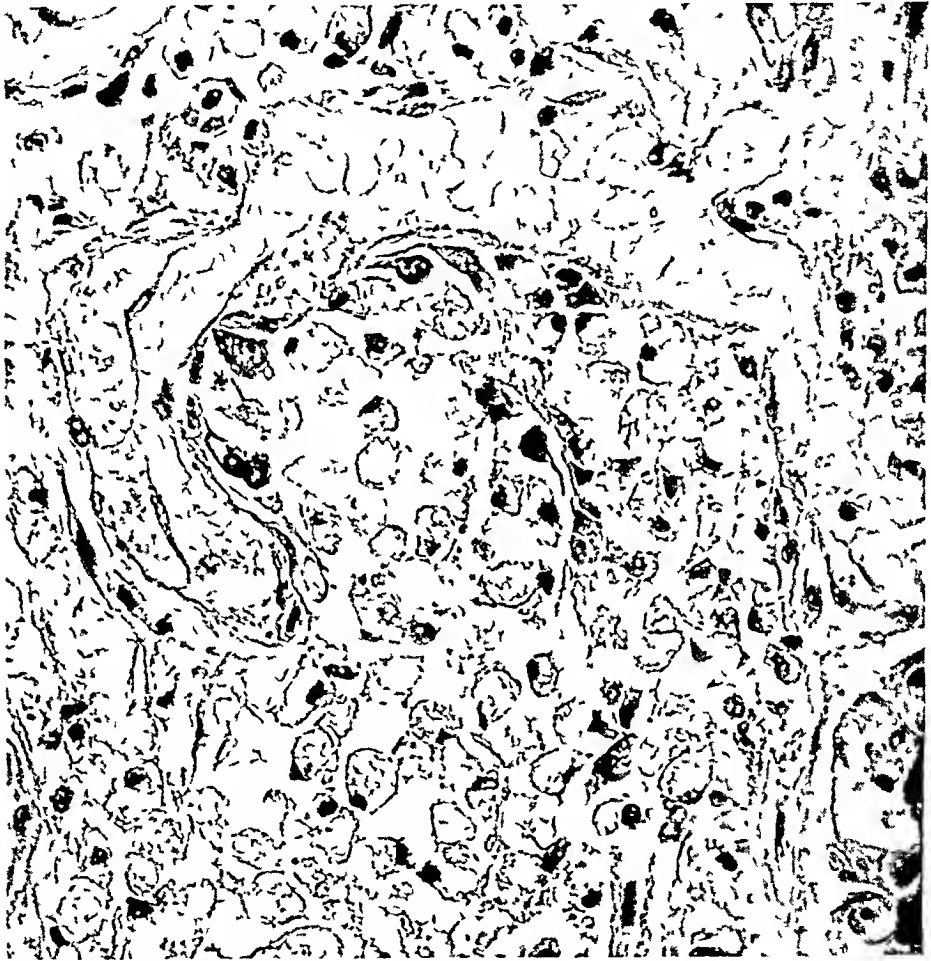


Fig 18—Macrophage reaction in the brain tissue adjacent to a metastatic nodule. Some of the macrophages lay close to or are attached to the wall of the blood vessel and give the impression that they originate and separate off from the adventitia. Hematoxylin and eosin $\times 320$

a motor area of the brain resulting in jacksonian attacks, weakness or hemiplegia. Of the other three patients two complained of headaches and one became delirious at the onset and died one week later.

In six cases of the second group the onset as stated was less abrupt, in three of this group the first symptoms were those of involvement of the motor areas and in two the illness began with headaches. In one patient the symptoms were most indefinite and although an

intracranial lesion was suspected it could not be localized. Briefly stated, nine of the patients had as their initial symptom weakness of one extremity, convulsive seizure or hemiplegia and four complained of headaches first.

Physical Examination The patients were not emaciated, nor did they show a marked loss of weight. No noteworthy abnormal observation was recorded in the examination of the thoracic organs, except in the case of two patients seen in

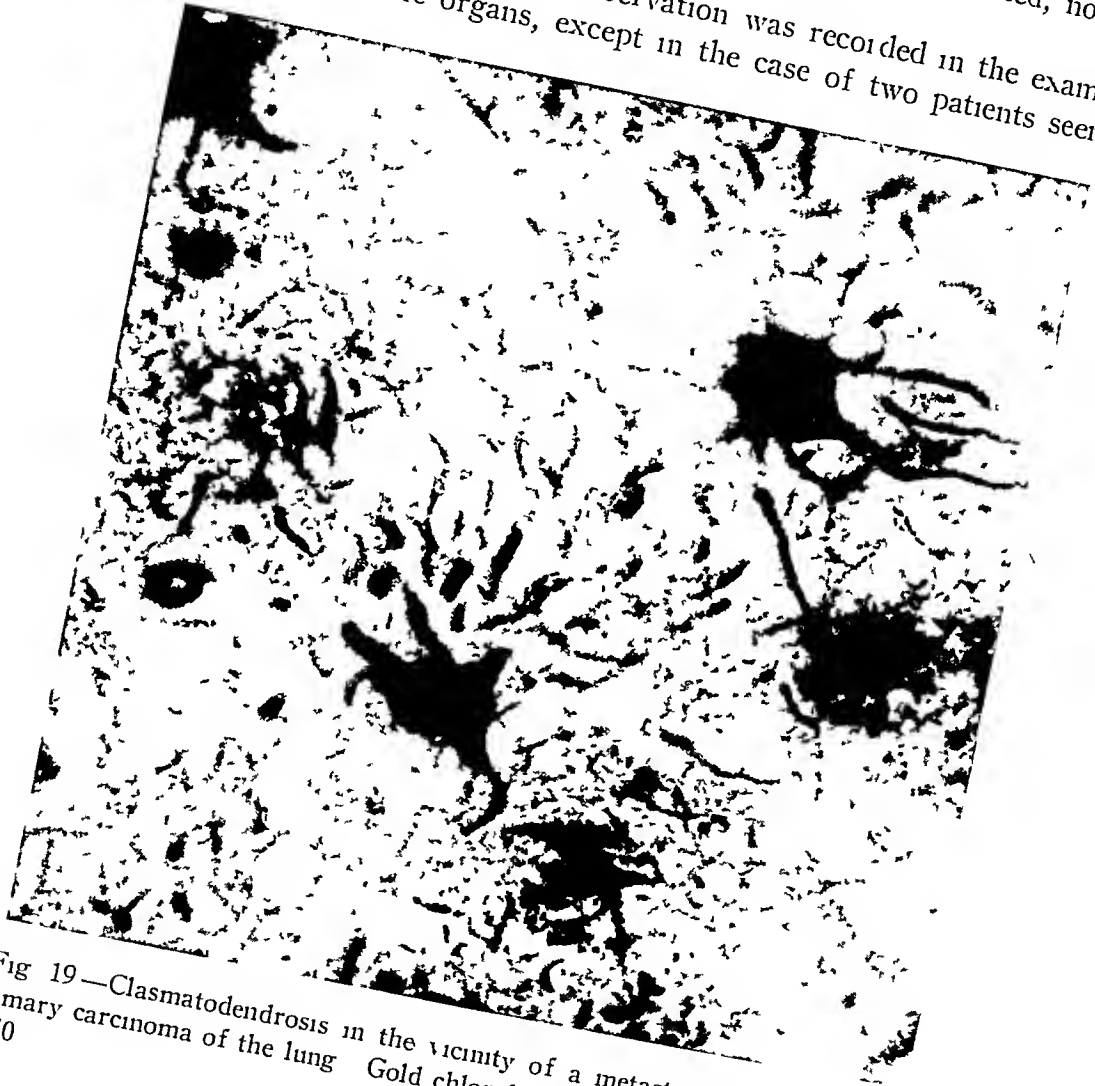


Fig 19—Clasmotodendrosis in the vicinity of a metastasis to the brain from a primary carcinoma of the lung. Gold chloride sublimate (Globus modification), $\times 850$

other hospitals in whom the physical signs were those of a lesion in the lungs compatible with pulmonary tuberculosis. In some of these cases there was evidence in the new formation of tissue that the choked optic disks had been present for some time. These observations are not in accord with those recorded in the literature that choking of the optic disks is

uncommon or that it occurs late in the course of the illness from a metastatic lesion to the brain

From the results of the neurologic examination a cerebral lesion was correctly localized in eight of eleven cases and this was confirmed in each instance by an intracranial operation. In each of these eight

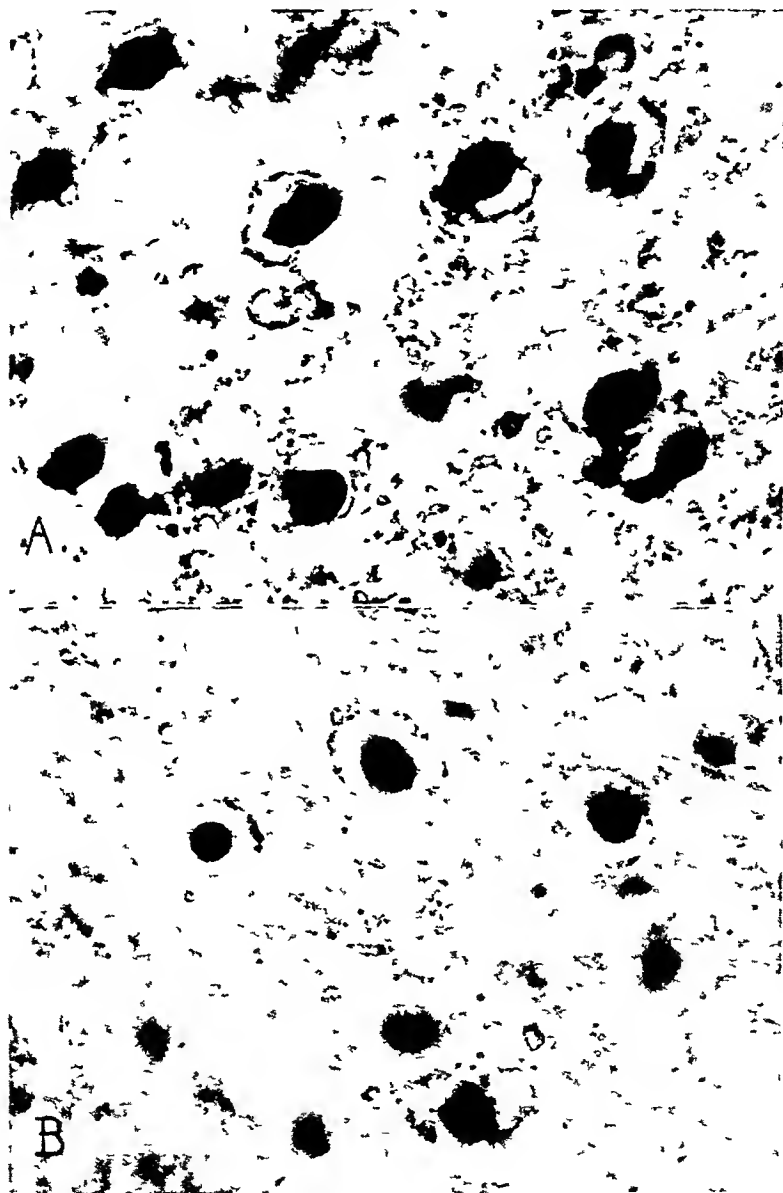


Fig 20—Swelling of the oligodendroglia in the brain with metastases from a primary carcinoma of the lungs (*A*) in the cerebral tissue close to the metastatic nodule, (*B*) in the edematous cerebrum at a distance from the metastatic nodule. Stain same as described under figure 19, $\times 850$

cases, the metastatic lesion was found in or near the motor area. Localizing signs were not definite in three cases. In one of these, a ventriculogram was made and a multicystic tumor was located. Subtemporal

decompressions were made in the remaining two cases and eventually the signs of a tumor manifested themselves, and metastases were removed at further operation

Course of Illness The course of illness was rapid in each case, so that the average period from the time of the onset of symptoms until hospitalization was but three months. One patient died one week from the onset of the intracranial symptoms, and two patients were ill for five months before being hospitalized

Signs of increased intracranial pressure occurred early in the course of the illness in the majority of the patients. In ten of the eleven cases in which operation was performed, one metastatic nodule was removed, and in two instances a similar nodule was again removed from the same location after recurrence six months or a year later. In one patient no tumor was found. In this instance, the marked edema of the brain prevented a thorough exploration

Five of the patients died within two weeks of the operation, and at necropsy the brains of four of these showed multiple metastases

Four patients lived five months, seven months, two years and seven years after the operation, respectively, with complete relief from their intracranial symptoms until the final overwhelming spread of the disease followed by rapid death

With the foregoing facts in mind, it is the opinion in this clinic that as a rule surgery is indicated in such cases, even though one is conscious that the lesion is a metastasis. For in instances in which the intracranial lesion was solitary, its removal with the leaving behind of the usual decompression has led to a prolongation of the patient's life and has spared him much suffering caused by an expanding intracranial lesion

SUMMARY

Metastases to the central nervous system were found in fifteen of thirty-seven patients with bronchiogenic cancer. For eleven of the fifteen patients, a diagnosis of primary tumor of the brain was made, and the bronchiogenic tumor was overlooked. For the remaining four patients, a definite diagnosis could not be made

An intracranial operation was performed on eleven of the patients, and a metastatic tumor was removed in ten instances

The postoperative survival period of the patients with solitary cerebral metastasis varied from five months to seven years (case 5). An early postoperative fatality resulted in every patient with multiple cerebral metastasis

It is believed that when a person of middle age has an abrupt onset of symptoms and signs of a rapidly developing intracranial lesion, a metastatic cerebral lesion should be thought of and that the lungs are

the most common site of the primary lesion. It is realized moreover that even in instances in which the examination of the lungs yields negative results the presence of a primary tumor in these organs cannot be excluded.

A metastasis to the brain from a primary pulmonary tumor was commonly mistaken for a rapidly growing glioma, a cerebral vascular lesion or an encephalitis.

Apparently the pulmonary tumor metastasizes to the brain by way of the blood stream. The relatively great frequency of intracranial metastasis is due in all probability to the fact that a tumor embolus from a pulmonary cancer passes from the pulmonary vein directly into the cerebral circulation, whereas cancers from other viscera on their way to the brain are primarily retained by the lungs, where they may remain indefinitely, often being altogether destroyed.

There is an outstanding reaction on the part of the microglia and astrocytes to the metastatic lesion, the response being very much like that found in experimental studies on the reaction of the brain to wounds and to infectious invaders.

HEMANGIO-ENDOTHELIOMA OF THE LIVER *

RAYMOND H GOODALE, M D

BEIRUT, SYRIA

Relatively few cases of hemangio-endothelioma of the liver have been reported, and it seemed advisable to add this case to those already on record because of the difficulty of clinical diagnosis and the interesting pathologic picture. The case was that of an emaciated child 11 months old with a marked enlargement of the liver of unknown origin.

REPORT OF CASE

History—A boy, 11 months of age, was brought to the hospital showing marked swelling of the abdomen of five months' duration. When the swelling was first noticed, the parents took the child to a physician, who prescribed quinine. The swelling continued, however, and there was no improvement. The patient was then brought to the dispensary, where it was found that the liver was enlarged and extended to 10 cm below the costal border. The spleen was also enlarged and extended down to the same level. Both organs were smooth on palpation at this time. A few discrete, firm glands were palpable in the axillae and the neck. The child returned to his home in Damascus and received frequent injections of quinine with apparent benefit, but the swelling of the abdomen continued to increase rapidly. The child continued to nurse well, did not vomit or have diarrhea and only occasionally had fever.

The patient entered the hospital about two months after his visit to the dispensary. On physical examination, he was found to be fairly well developed and nourished. The abdomen was enormously distended, and a network of dilated veins was visible over the upper part of the abdomen. The lower edge of the liver was palpable 8 cm above the symphysis pubis. The liver was covered with fluctuant nodules averaging 3 cm in diameter. There was considerable fluid in the lower part of the abdomen. No tenderness or rigidity was elicited.

Laboratory Observations—The red blood cell count was 2,840,000, the hemoglobin content (Tallqvist) was 60 per cent. The white blood cell count was 6,900. The differential count gave polymorphonuclears, 68 per cent, lymphocytes, 30 per cent, monocytes, 1 per cent, and transitionals, 1 per cent. The Wassermann reaction was negative. The mother's Wassermann reaction was 1+.

Autopsy—The body was that of a fairly well developed and poorly nourished male infant with a markedly distended abdomen. The skin over the abdomen was tense and shiny, and the umbilicus was everted. The liver was easily palpable, and the lower edge was felt at a point in the midline about 10 cm above the symphysis. Multiple soft nodules could be palpated on the liver surface.

When the abdomen was opened, a large nodular liver was found occupying the entire right side. A liter (1,000 cc) of clear yellow fluid was taken from the pelvis.

* Submitted for publication, Nov 7, 1929.

* From the Department of Pathology, American University of Beirut.

The liver weighed 1 100 Gm. It was covered with purple nodules varying in size from that of a marble to that of a horse chestnut. These nodules stood out on a dull yellow background of liver substance, and were soft on palpation. Some were flat, others were umbilicated. On section these dark red areas were found throughout the liver, replacing practically the entire organ (fig 1). The small amount of liver tissue remaining was yellow. The nodules were hemorrhagic and were apparently surrounded by a band of white connective tissue.

The other observations at autopsy were enlarged mesenteric glands and a stone the size of the head of a pin in the upper part of the left ureter. No metastases of the tumor were found.

Histologic Examination—Pieces of tumor and liver tissue were fixed in Kaiserling I solution and were stained with hematoxylin and eosin and with van Gieson's connective tissue stain.



Fig 1—Liver showing tumor nodules (a) and liver tissue (b)

Some tumor nodules were made up of dilated blood spaces separated by bands of connective tissue in which no liver cells were seen. The blood spaces were lined with endothelial cells, which appeared larger and more numerous than those of a normal blood vessel (fig 2). The outlines of these cells could not be seen, but the nuclei stained a pale or deep blue and stood out against a pale pink cytoplasm. The nuclei were vesicular and oval or fusiform. No mitotic figures were seen. There was no evidence of hematopoiesis. The blood spaces were filled with red blood cells mixed with a normal number of leukocytes.

Other sections of the tumor showed a different picture. Under low power, the tissue appeared to be a solid mass of tumor cells with many tiny openings. Under high dry power, these tiny openings were found to be surrounded by single cells. These were apparently attempts to form blood vessels, for red blood cells were found in some of them. In many places were concentric blue-staining masses similar to those seen in dural endothelioma. Some fields showed small solid

masses of endothelial cells which had not formed blood vessels. The tumor nodules, in general, were found to be surrounded by connective tissue in which were a few atrophic liver cells.

A few foci of lymphocytes were found in the increased connective tissue around the bile ducts. The branches of the hepatic artery showed swelling of the endothelial cells. The liver cells showed albuminous degeneration, but were otherwise normal.

The diagnosis was congenital hemangio-endothelioma of the liver.

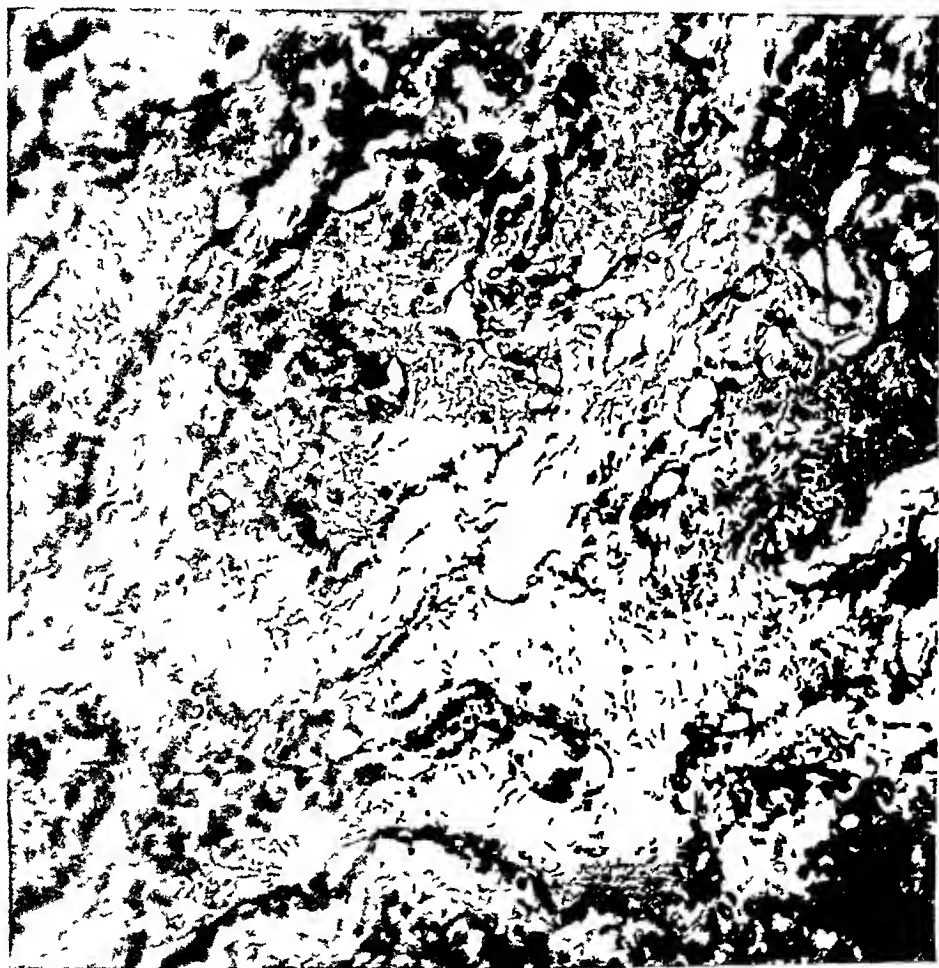


Fig 2—Section of tumor nodule showing blood spaces lined with endothelial cells.

THE LITERATURE

Foote¹ reported a case and reviewed the literature on congenital hemangio-endothelioma of the liver in 1919. He suggested that these tumors be called hemangio-endothelioma because they were the result of rapid and unrestrained proliferation of the endothelium of the capillaries of the liver. From the ten reports of cases which he reviewed, Foote concluded that such a tumor was a congenital disease.

¹ Foote, I. Hemangio-Endothelioma of Liver, *J A M A* **73** 1042 (Oct 4) 1919.

manifesting itself by hepatic enlargement and some digestive disturbances within three months after birth. There was a fatal termination in every case before the patient was 6 months of age. The patient in the case described in this paper, however, lived until the eleventh month.

Foote¹ stated further that jaundice and ascites were not usually observed, and that metastases were not found. The liver was purplish and studded with nodules varying in size from that of a millet seed to that of an egg, some of which were confluent. These nodules were lighter in color than the surrounding tissue and throughout the liver in cut section had in each instance a dark red center surrounded by a lighter colored ring. Histologically the liver showed an infiltration of the normal areas with small round cells. In places, the liver cells were distorted, atrophied and vacuolated. The interlobular connective tissue was increased. The smaller blood vessels were choked with large endothelial cells, some showing mitotic figures. The nodules were surrounded by a fibrous band of compressed liver tissue. In some places, this fibrous band showed lacunae containing degenerated liver cells. The larger nodules were packed with large round or irregular cells with large nuclei, some areas resembling myxosarcoma. Giant cells and polymorphonuclears were also seen in some areas.

Godel² described the condition of a child 3 months old with multiple primary tumors in the liver which he diagnosed hemangio-endothelioma. The liver was 15 by 8 by 4.5 cm. and yellowish brown. Many nodules were seen through the capsule; they were the size of a hazelnut and smaller. On section the nodules stood out bluish gray against the liver tissue. The microscopic picture was essentially the same as that reported in the liver here described.

Another case described by Orzechowski³ differed in three particular features from any of the cases reports of which have thus far been published. The subject, a girl 2½ months old, was markedly icteric and the liver parenchyma was greenish indicating severe stasis of the bile. This hemangio-endothelioma had metastasized to the lung and to the skin, with multiple lesions in each organ. The third distinguishing feature was blood cell formation in the tumor nodules in the liver. This included the formation of both red and white blood cells and would indicate a continuation of the hematopoietic function of the liver from fetal life.

In none of the other cases reported in the literature thus far was icterus or hematopoiesis in the tumor of the liver observed. Hewlett⁴

2 Godel, A. Frankfurter Ztschr. f. Path. **29** 375 1923

3 Orzechowski, G. Virchows Arch. f. path. Anat. **267** 63 1928

4 Hewlett. Intercolon. M. J. Australia **4** 615 1899

was the only other author to report metastases from sarcoma of the liver in a case that may have been one of hemangio-endothelioma. He mentioned nodules in the lungs of the same general microscopic appearance as those in the liver, but he did not give the details of their structure.

Bondy⁵ reported a case clinically which might be classified as one of hemangio-endothelioma. The child had a protuberant abdomen, especially in the right upper quadrant, which was first noticed by the mother when the child was 3 weeks old. The circumference of the abdomen at this time was 18 inches (45.72 cm) at a point 1½ inches (3.77 cm) below the costal border. Percussion over the upper three quarters of the abdomen gave a flat sound. On palpation, an indistinct mass was felt filling both sides of the upper part of the abdomen. The surface of the mass was smooth, and the edge was distinctly palpable below the umbilicus. This mass could not be definitely connected with any organ.

At operation, an enormously enlarged liver was found, filling three quarters of the abdominal cavity. The liver was dark brown and was mottled with small blue areas, averaging 1 cm in diameter. The surface was smooth. The spleen and the kidneys were not enlarged, nor was there any invasion of any other organ. The child died at the age of 3½ months with a girth of 29 inches (73.66 cm) at the umbilicus. No autopsy was permitted.

A piece of the liver was removed at operation, and the microscopic diagnosis was angiosarcoma. No description of the sections was given, so that one cannot conclude definitely whether or not the tumor fitted into the category of hemangio-endothelioma. The clinical picture, however, was similar to that in the cases thus far reported in the literature.

COMMENT

Various theories have been put forth in an attempt to explain the angiomatosis of the liver. Schmieden⁶ believed that for the majority of such tumors, a simple dilatation of the capillaries affords an adequate explanation. Ribbert⁷ also believed in the factor of capillary dilatation, but he maintained that this is secondary to embryogenic disturbances of the endothelium. I believe that in the case presented in this article the tumor was a true blastoma of endothelial cells. Some sections had the appearance of a simple cavernous hemangioma, while others had the appearance of an endothelioma. Mallory⁸ stated that

5 Bondy, J. Angiosarcoma of the Liver in an Infant. *J. A. M. A.* **56**: 373 (March 25) 1911.

6 Schmieden. *Virchows Arch. f. path. Anat.* **161**: 373, 1900.

7 Ribbert. *Virchows Arch. f. path. Anat.* **102**: 351, 1898.

8 Mallory, F. B. *Pathology of Malignant Diseases of Nonepithelial Formation*. *J. A. M. A.* **55**: 1621 (Nov. 5) 1910.

tumors arising from endothelial cells should be called endotheliomas. Most pathologists, however, reserve this term for the rapidly growing tumors and speak of the slow-growing ones as angiomas. In another article, Mallory⁹ proposed the name hemangio-endothelioma for those angiomas which show definite proliferation of endothelial cells and new formation of blood vessels.

Ewing¹⁰ did not use the term hemangio-endothelioma of the liver. He called the tumor reported by Veeder and Austin¹¹ as hemangio-endothelioma, a multiple congenital hemangioma of the liver.

The sections of the tumor here described which show masses of endothelial cells indicate a more active and malignant tumor than the simple hemangioma which is seen in some of the sections in this case. It seems, therefore, that the term hemangio-endothelioma is correct for this tumor.

SUMMARY

A case of multiple congenital hemangio-endothelioma of the liver in a male infant 11 months old is described. The total number of such tumors reported in the literature to date is fourteen including that described in this paper.

9 Mallory, F. B. *J. Exper. Med.* **10** 575, 1908.

10 Ewing, J. *Neoplastic Diseases*, ed. 3, Philadelphia: W. B. Saunders Company, 1928, p. 249.

11 Veeder and Austin. *I. M. Sc.* **143** 102, 1912.

VENTRAL SYMMETRICAL HYPEROSTOSES OF THE INNER TABLE OF THE CALVARIUM*

LEROY W. YOLTON, A.M.

CHICAGO

Occasionally, at autopsy, symmetrical thickenings of the inner table of the ventral portion of the calvarium are observed. These hyperostoses are more or less irregular in contour and are thickest within that portion of the frontal bones corresponding to the frontal eminences. The growths, when extensive, also involve parts of the adjacent parietal bones, but they characteristically avoid the orbital portion of the frontal bone and also the sagittal sulcus. They may be compact in structure or contain spongy diploe. The vascular channels are generally deep grooves or occasionally tunnels in the new bone. The high proportion of incidence in females is remarkable. The hyperostoses are symptomless and are rarely if ever diagnosed during life.

The literature of the last ninety years contains a number of references to this condition under various names. One of the early descriptions is in the catalog of the Musée Dupuytren¹ in which there are also three lithographic illustrations. There is minor mention of this type of hyperostosis by Bucknill and Tuke,² Birkett,³ Clouston,⁴ Lewis,⁵ Humphrey,⁶ Beadles⁷ and Shattock.⁸ Of greater interest are the con-

* Submitted for publication, Nov. 7, 1929.

* From the Norman Bridge Pathologic Laboratory, Rush Medical College.

1 *Museum d'anatomie pathologique de la Faculté de médecine de Paris, ou Musée Dupuytren*, Paris, Bechet jne et Labe, 1842, vol. 2, pp. 503-505, atlas, pl. 15, figs. 5, 6 and 7.

2 Bucknill, J. C., and Tuke, T. H. *Manual of Psychological Medicine*, Philadelphia, Lindsay and Blakiston, 1874, p. 567.

3 Birkett, J. *Contributions to the Practical Surgery of New Growths or Tumours. Series VI. Cartilaginous and Bony Growths*. *Guy's Hosp. Rep. (Series 3)* **14**: 475 (pl. 4, fig. 3) 1869.

4 Clouston, T. S. *Clinical Lectures on Mental Diseases*. Philadelphia, Henry C. Lea's Son & Company, 1884, pp. 407-408, *ibid.*, ed. 6, 1904, pl. 29.

5 Lewis, W. B. *Textbook of Mental Diseases with Special Reference to the Pathological Aspects of Insanity*, London, C. Griffin & Company, 1889, p. 433.

6 Humphrey, G. M. *Senile Hypertrophy and Senile Atrophy of the Skull*, *Med. Chir. Tr.*, London **73**: 327, 1890.

7 Beadles, C. F. *The Cranium of the Insane*, *Edinburgh M. J. (N. S.)* **3**: 263, 1898.

8 Shattock, S. G. *Morbid Thickening of the Calvaria, and the Reconstruction of Bone Once Abnormal, a Pathological Basis for the Study of the Thickening Observed in Certain Pleistocene Crania*, *Tr. Internat. Cong. Med.*, 1913, sec. 3, pt. 2, London, 1914, pp. 17-25, and pl. 3, figs. 1-5.

tributions by Rokitansky⁹ Naito and Schuler,¹⁰ Naito¹¹ Knaggs¹² and Stewart¹³ The most extensive studies are those by Engel,¹⁴ Dressler¹⁵ and Grieg¹⁶ In these writings there is reported a total of 165 instances of this abnormality of the frontal region In 113 of the cases the patients were females and in 15 males In 37 instances, the sex was not known Dressler reported that in 1 632 autopsies he found 71 of these hyperostoses or 4.35 per cent, 64 of which were in females and 7 in males Grieg examined 188 calvaria the sexes being practically equal and found 32 with the hyperostoses 28 being in females and 4 in males Thus, in one large series, the incidence was over 4 per cent and of these nearly 90 per cent were in females

In the museum of the Norman Bridge Laboratory of Pathology at Rush Medical College there are four calvaria bearing these hyperostoses

No 314-21—This specimen is a skullcap (fig 1) from an autopsy performed by Dr E R LeCount on the body of a white man aged 64 who died from chronic alcoholism and bronchopneumonia It weighs 384 Gm and is 18.9 cm long 13.7 across and 8 high Externally, the contour is regular, and the suture lines are partly obliterated, the metopic suture entirely so Wormian bones are present in the lambdoid and coronal sutures An eburnated exostosis, 3 by 4 mm and raised 0.5 mm, is present 1 cm above the anterior sawed edge of the frontal bone 2 mm to the right of the midline There are delicate vascular grooves in the middle of either lateral half of the frontal bone from 0.5 to 2 cm above the sawed edge Minute vascular openings in the outer table are associated with these grooves

Internally, all suture lines are obliterated, and the frontal region is covered by a bony thickening The edge made by sawing measures 14 mm at its thickest place in the right frontal region, in the left, 11 mm In the occipital region, it averages usually about 4 mm The contour of the hyperostoses medially is wart-like with small knobs and granules arising abruptly The lateral portions are more regular in contour and come down gradually to the level of the rest of the inner table slightly beyond the coronal suture The midline is avoided, so that ventrally

9 Rokitansky, C. A Manual of Pathological Anatomy, Sydenham Society Translation, London, 1850, vol 3, pp 127, 129, 133, 211 and 378 This is a translation of the German edition of 1842

10 Naito, T, and Schuler, A. Ueber die Hyperostosen des Schädels. *Wien klin Wchnschr* 36 792, 1923

11 Naito Inasaburo. Die Hyperostosen des Schädels, Vienna and Leipzig, Josef Šafař, 1924, pp 75-81

12 Knaggs, R L. The Inflammatory and Toxic Diseases of Bone, New York, William Wood & Company, 1926 pp 205-207

13 Stewart, R M. Localized Cranial Hyperostosis in the Insane, *J Neurol & Psychopath* 8 321, 1928

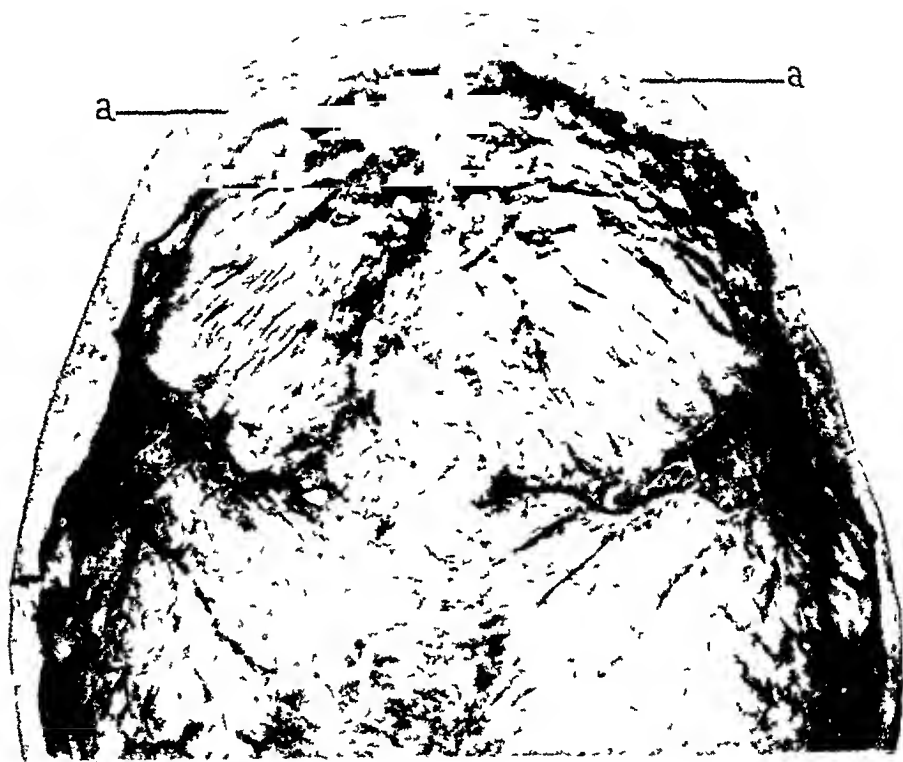
14 Engel, J. Das Osteophyte an der inneren Schädelfläche, *Wien med Wchnschr* 21 770, 794 and 823, 1871

15 Dressler, L. Ueber die Hyperostosen des Stirnbens, *Beitr z path Anat u z allg Path* 78 332 1927 This contains a critical review of the literature, and the reader is referred to this article for additional references

16 Grieg, D M. Intracranial Osteophytes. *Edinburgh M J* 35 165 and 237, 1928

at the sawed edge there is a narrow groove resembling a saw-cut, 1.5 mm wide, flanked by steep sides 5 mm high. At the surface, the groove is narrower, 1 mm, and at the bottom the walls are slightly undercut. The median free space widens out toward the bregmatic region, where it is 2.5 cm wide. In the middle of this triangular free space is the shallow groove for the sagittal sinus and beside it depressions for the paccionian bodies. The bregmatic region is no thinner than the nearby portions of the vault. The channels for the middle meningeal vessels are deep, particularly near the edge of the hyperostoses, and in places they become tunnels in the bone.

The surfaces of the hyperostoses are marked with elongated pits and fine wrinkles approximately parallel, but converging toward a point in the midline about 2 cm above the ventral sawed edge. However, at the margins of the



The ventral portion of calvarium no 314-21 illustrating the symmetrical hyperostoses of the inner table: the knoblike and the more diffuse portions of the growths, their avoidance of the midline, the inner boundary of the inner table (a) under the growths and the vascular furrows in the parietal regions.

growths, near the coronal suture, these streaks run in a coronal direction. The surface texture is smooth almost polished.

Where the saw-cut passes through the hyperostoses, the compact outer table is from 1 to 1.5 mm thick. Next is the diploe, a zone of spongelike structure measuring about 2 mm. Then comes an ill defined compact layer slightly more than 1 mm thick, evidently representing the original inner table, and this is followed by the hyperostosis. The latter is made up of a spongy layer as much as 8 mm thick, slightly more porous than the normal diploe, and covered by a thin, hard layer, less than 1 mm thick, forming the inner surface. At the edges of the growth, the innermost layer fuses with the inner table of the skull by disappearance of the spongy layer.

In the other three calvaria concerning which there are no records there is not as much adventitious bone

No 314-23—This skullcap measures 187 by 141 by 83 cm and weighs 542 Gm. Externally all suture lines are distinct and a metopic suture is present. The skull is generally thick and in the region of the vertex it measures 1 cm. The inner portion of the frontal region is humpy in contour but the texture of the surface is smooth and hard. On the sawed edge the thickest places measure 12 mm, on the right and 10 on the left. The occipital region is about 6 mm thick though in the region of the internal occipital protuberance it is over 10 mm thick. In the frontal region, the inner table is not traceable under the hyperostosis but the area is uniformly spongy. The sagittal region is thinner than the frontal squamas.

No 314-24—This calvarium has all suture lines obliterated except the coronal suture which is present for about 25 cm on the right and 4 cm on the left between the superior and inferior temporal lines. It weighs 300 Gm and measures 18 by 148 by 76 cm. Internally there is an increase in the thickness of the frontal squamas so that the usual concavity there is made nearly flat, though gently undulating. There are four rounded knobs near the medial border of the left hyperostosis. The thickest place along the sawed edge on the left is 13 mm thick, on the right, 8 mm. However on the right, the saw-cut was below the main part of the hyperostosis. The midline is not thickened. The furrows for the middle meningeal arteries are deep and are converted into tunnels for short distances 2 mm on the left 15 on the right. The rhomboidal bregmatic region is slightly thicker than the surrounding region and this impression is accentuated by the pits for the arachnoid granulations around it. The surface of the hyperostoses is smooth, except for fine striations.

No 314-25—This skullcap is 18 by 133 by 78 cm, in dimensions and weighs 442 Gm. All suture lines are obliterated, except about 15 cm of the coronal suture on both sides between the temporal lines. The specimen impresses one as unusually heavy. The edge is nowhere very thick but the frontal concavities are filled with bone presenting a wavy surface. The thickest portion on the left is 12 mm thick, on the right, 11 mm. This thickening is diffuse, and the midline is not notably depressed below the level of either side. A depression for the main trunks of the middle meningeal vessels toward the bregma separates this region from pronounced thickenings of both parietal bones. These hyperostoses are irregular in outline and more irregular in contour than the frontal hyperostoses. The one on the right is 16 mm thick that on the left, 13 mm. Both drop off abruptly toward the midline and ventrally. Elsewhere, the edges slope down gradually to the surrounding level. A space from 2 to 3 cm wide in the midline is not covered by these. There are deep grooves and in places tunnels in these growths for branches of the middle meningeal vessels. In the median longitudinal sulcus in the dorsal half of the parietal region, there are small irregular points and scales projecting a millimeter or so from the surface. The longest scale is 10 mm long and 2 mm wide. These appear to be delicately and superficially adherent to the underlying surface.

One of the earliest and most persistently repeated explanations of the etiology of these ventral hyperostoses is that by Rokitsansky.⁹ He suggested that the bone deposit is compensatory for atrophy of the

brain, either occurring in senility or occurring prematurely "as a consequence of mental diseases which are characterized by excitement" This point of view is elaborated by Engel,¹⁴ and essentially similar opinions are expressed by Clouston,⁴ Humphrey,⁶ Beadles,⁷ Shattock,⁸ Naito and Schulei¹⁰ and Naito¹¹ Some of these, however, believe that hyperemia of the skull bones or dura is also an important factor and that this is brought about by such conditions as recurrent attacks of maniacal insanity or epilepsy However, Grieg¹⁶ reported that the mental condition of the persons represented in his series was "perfectly normal for the social position these people occupied during life" Lewis⁵ thought that inflammation plays a part, and Knaggs¹² suggested explaining the hyperostoses on an inflammatory basis as arising from toxins, as he does pulmonary osteo-arthropathy On the other hand, the absence of inflammatory change is attested by Dressler¹⁵ and inferred by others Theories based on disturbances of the endocrine glands are advanced for all sorts of diseased conditions, and Stewart¹³ ventured that one may be "dealing with a hitherto undifferentiated type of dyspituitarism"

Grieg¹⁶ approached the compensatory theory from a chemiophysiology point of view and concluded that the hyperostoses are a result of disuse absorption of calcium and phosphorus from other parts of the skeleton in excess of existing excretory powers and that this excess is deposited in the frontal region as "an innocuous relief to a system supersaturated with calcium in an area which age renders least important"

Because there was no more than slight atrophy of the frontal lobes associated with any of the seventy-one calvaria studied by Dressler,¹⁵ he was led to believe that a prolonged illness may cause the compensatory hypertrophy of the frontal bones by the dorsal sinking of the brain while the patient is confined to bed He said that the midline is avoided in the new bone formation because the relations of pressure, in spite of the increased weight on the tentorium, do not affect the attachments of the tightly spread falx cerebri He found long drawn out sickness in most of the histories

The preponderance in females is missed by Engel,¹⁴ but conceded by other observers Beadles⁷ thought it was due to the longer residence in the insane asylum by the female inmates Dressler¹⁵ attributed it to the earlier onset and more marked degree of atrophy of the brain in females with a possible temporary predisposition during pregnancies when, he supposed, there is a slight relative anemia of the brain and a "hormonal stimulus" that causes an increased proliferative reactivity of the bones However, its occurrence in nulliparae, as well as in males, is emphasized by him and confirmed by Grieg¹⁶

SUMMARY

Ventral symmetrical hyperostoses of the inner table of the calvarium are much more frequent in women than in men. There is a notable absence of full details of the illnesses which possibly may be associated with this overgrowth of bone. In the most attractive explanation so far advanced, compensation for atrophy of the brain in a "system supersaturated with calcium," many essentials needed to make it satisfactory are absent.

Historical and General Reviews

THE DETERMINATION OF THE INFECTIOUS NATURE OF ACUTE ENDOCARDITIS

IN COMMEMORATION OF THE FIFTIETH ANNIVERSARY OF THE
CHICAGO PATHOLOGICAL SOCIETY

LUDVIG HEKTOEN, M D
CHICAGO

AN EPISODE IN THE CHICAGO PATHOLOGICAL SOCIETY

On March 24 1879, Dr Chris Fenger, pathologist to the Cook County Hospital exhibited some morbid specimens obtained from a recent patient. When he opened the body, the doctor had no history of the case except that the patient presented typhoid symptoms. Opening the abdomen he found infarctions in the submucous tissue of the intestines, in the spleen and in the kidneys. The source of these emboli was found in an ulcerous endocarditis both sets of semilunar valves presenting an abundant deposit. Upon examining farther, an embolus was found in the left middle meningeal artery which had caused an extensive infarct, and several small infarcts were found in each retina (illustrating the value of the ophthalmoscope in the diagnosis of heart disease). The doctor thought from the fact that some of the infarcts were breaking down into abscesses that the cause of endocarditis was septicemia. There was no evidence of acute rheumatism nor of any surgical operation. Careful search, however, revealed a suppurating synovitis at the bottom of a large bunion. Dr Fenger said this might have been the starting point of the whole disease. As a proof that this was a blood disease the doctor exhibited under the microscope some of the exudate from the heart valves in which were myriads of micrococci."

This report¹ was prepared by William T Belfield a pioneer American student of bacteriology. What interest has this report besides illustrating Fenger's power as pathologist? The report is remarkable because it is if not the first, one of the first demonstrations in this country of the infectious nature of acute endocarditis. A brief resume of the events that led to the establishment of the true nature of acute endocarditis will set forth the significance of Fenger's demonstration fifty years ago.

BOUILLAUD TO VIRCHOW

I shall not try to trace the earliest beginnings of knowledge about endocarditis. It begins with records and illustrations which show that the condition was observed at postmortem examinations. Many early observations of endocarditis are mentioned in the books, Cowper

1 Fenger, Christian. Chicago M J & Examiner 38 496, 1879

Morgagni Sandifort Baillie and Alan Burns were some of the pioneer observers. The illustrations by Sandifort¹ are striking and his legends are precise but he could not fully understand the lesion that he recorded. The connection between acute endocarditis and rheumatic fever pneumonia and other infectious states did not escape the notice of early observers. Morgagni, for instance observed it in association with gonorrhea. But endocarditis remained a closed book until the nineteenth century. It was Bouillaud² the great French clinician who first pointed out clearly and comprehensively the anatomic and clinical characteristics of acute endocarditis. He set up two forms the simple, frequently associated with acute articular rheumatism, and the typhoidal in septic or putrid diseases. In the main this view has prevailed. Years passed before any new light was thrown on these conditions. In the meantime, the interest in the nature of suppuration and infection grew and active search was made for the agents or poisons concerned.

In 1843, Vogel³ described and figured "vibrios which develop in enormous numbers in all decomposing fluids in decomposing blood in decomposing eggwhite etc, and which hardly ever are absent in foul ulcers." Vogel's figures will be referred to again. The word vibrio or vibron is used frequently in early descriptions of microbes without the special meaning given to it later, but as synonymous with mobile bacterium. Somewhat later vibrios "Kugelbakterien" micrococcal masses and colonies "granulations" were described as occurring in purulent and pyemic lesions. Mayrhofer claimed that puerperal infection was due to vibrios which he found abundantly in the lochia. In 1879, Pasteur⁴ said that he had seen streptococci ("petits chapelets de grain spheriques") in 1860. Rokitsansky,⁵ Oertel, Waldeyer, Rindfleisch⁶ von Recklinghausen Klebs⁷ and Orth⁸ observed bacteria in human lesions. Apparently on the basis of the following statement,

1a Sandifort, Edward. *Observationes anatomico-pathologicae*, Lugdun Batavorum, 1757.

2 Bouillaud, Jean-Baptiste. *Traite clinique des maladies du coeur*, etc., Paris, 1835. *Traite clinique du rhumatisme articulaire et de la loi de coincidence des inflammations du coeur avec cette maladie*, Paris, 1841.

3 Vogel, Julius. *Erlauterungstafeln zur pathologischen Histologie* 1843.

4 Pasteur, Louis. *Bull Acad de med* **81** 256, 1879.

5 Rokitsansky, Carl. *Lehrbuch der pathologischen Anatomie*, ed 3, 1855, vol 1, p 387.

6 Rindfleisch, Eduard. *Lehrbuch der pathologischen Gewebelehre*, 1867.

7 Klebs, E. *Weitere Beiträge zur Entstehungsgeschichte der Endocarditis*, *Arch f exper Path* **9** 52 1878.

8 Orth, Johannes. *Untersuchungen über Puerperalfieber*. *Virchows Arch f path Anat* **58** 473, 1873.

Rokitansky⁷ has been given credit as the first to describe bacteria in endocarditis

Einmal habe ich runde, langlichrunde, 1/66-1/25 mill im Durchmesser haltende, walzen- und wurstformige, 1/33-1/25 mill breite, bis zu 1/5 mill lange, aus einem hyalinen in Essigsäure löslichen, eine Menge von kleinen bei Einwirkung von Essigsäure schrumpfenden körnchen einschliessenden starren Eiweisskörper bestehenden Gebilde, vereinzelt und zu Knäulen unter einander verschlungen, in Fibringerinnungen im Herzen bei Pneumonie, und ein zweiter mal ähnliche in fibrinösen Vegetationen an der Valv bicuspidalis gesehen

This may be translated as follows "Once in fibrinous clots in the heart in pneumonia and a second time in fibrinous vegetations on the bicuspid valve I have seen round, oblong (from 1/66 to 1/25 mm in diameter), cylindric and sausage-shaped (from 1/33 to 1/25 mm broad, up to 1/5 mm long) formations of stiff, hyaline albuminous matter, soluble in acetic acid, occurring singly, as well as in twisted coils, and enclosing a multitude of small granules, which shrank under the influence of acetic acid

Klebs⁷ maintained that pyemia was caused by his *Mikrosporon septicum*, while diphtheritic (in the anatomic sense) processes were caused by a special fungus—a view to be opposed by Eberth⁹ Orth's description of chain-forming bacteria in the peritoneal exudate in peritoneal fever is particularly convincing⁸ It is well to recall that at this time special staining methods for bacteria were not available The observations were made on unstained preparations after fat and other material had been removed by rather drastic methods As example may be cited the statement by Orth as late as 1876 that there are numerous micrococcal colonies in ulcerative endocarditis which remain unchanged after boiling in absolute alcohol and ether followed by treatment with acetic acid¹⁰

Of chief concern in this article is ulcerative or malignant endocarditis, the gross and microscopic changes of which were described accurately by the middle of the last century The resemblance anatomically of the endocardial lesion in many cases to the so-called diphtheritic processes was recognized The frequent association of ulcerative endocarditis with puerperal infection with pyemia and with other infections was recognized fully but its relation to these conditions and their lesions was not yet explained A great advance was made when Virchow¹¹ completed his splendid doctrine of embolism and demonstrated in 1856

9 Eberth, C J Zur Kenntnis der bacteritischen Mykosen, 1872 Cor Bl f Schweiz Aerzte 2 248, 1872, Ueber diphtherische Endocarditis Virchows Arch f path Anat 57 228 1873 65 352, 1875 72 103, 1878

10 Orth, Johannes Compendium der pathologisch-anatomischen Diagnostik 1876

11 Virchow, R Ges Abhandl z Wissensch Med 1856, p 705 Zur pathologischen Anatomie der Netzhaut und der Sehnerven, Virchows Arch f path Anat 10 170, 1856

the embolic nature of the arterial plugs in malignant endocarditis. In the next year Beckmann¹² studied an instance of ulcerative endocarditis with capillary emboli in various organs. These emboli were minutely granular (aussest feinkörnig). Apparently independently of Virchow, Kirkes¹³ correctly interpreted the mechanical effects of the arrest in the circulation of solid particles detached from fibrinous deposits on the interior of the heart. Kirkes also had a notion that the general symptoms of ulcerative endocarditis were caused in some way by contamination of the blood by material from the diseased valves and that consequently a poisoned state of the blood analogous to pyæmia might result from ulcerative inflammation of the cardiac valves. A similar view was expressed by others at about this time. Watson¹⁴ after describing a case of ulcerative aortic endocarditis said "With such mischief in rapid progress within the heart it is easy to see how the blood may be polluted and charged with a new poison in its very fountain."

Anatomically ulcerative endocarditis resembles diphtheritic processes, said Friedreich¹⁵ in 1861 and may discharge a specific ichorous substance ("spezifische ichorose Substanz") into the blood where it may exercise chemically infective actions on the organism with most pernicious effects and a pyæmic typhoidal symptom complex. In the rheumatic form emboli have only mechanic effects.

Charcot and Vulpian¹⁶ referred to certain minute particles in ulcerative endocarditis as having septic qualities and causing symptoms of intoxication. And Rindfleisch¹⁷ who saw vibrios in miliaary abscesses in the myocardium put it this way: "Various abnormal conditions of mixture of the blood the pyæmic the puerperal the typhoidal blood mixtures above all the blood mixture in acute articular rheumatism act upon the endocardium as inflammatory stimulus." Rindfleisch described the gross and microscopic changes in endocarditis adequately and interpreted their local consequences clearly.

The master mind now in charge of developments was of course Virchow. The results of his experiments and observations on embolism

12 Beckmann, Otto. Ein Fall von kapillar Embolie, Virchows Arch f. path. Anat. **12** 59, 1857.

13 Kirkes, S. W. Ulcerative Inflammation of the Valves of the Heart in a Case of Pyæmia, Edinburgh M. & S. J. **18** 119, 1853, Med-Chir. Tr. **35** 281, 1852, On Ulcerative Inflammation of the Valves of the Heart as a Cause of Pyæmia, Brit. M. J. **2** 497, 1863.

14 Watson, Thomas. Principles and Practice of Physic, ed. 4, 1857 vol. 2, p. 315.

15 Friedreich, N. Die Krankheiten des Herzens, in Virchow, R. Handbuch der speziellen Pathologie und Therapie, 1861, vol. 5 (pt. 2), p. 322.

16 Charcot, J. M., and Vulpian, A. Note sur l'endocardite ulcéreuse aigue de forme typhoïde, Gazette med., Paris **33** 386, 1862.

demanding explanation. Virchow himself at first thought that the suppuration in some instances of embolism was due to the chemical nature of the emboli themselves or of the subsequent changes in them. This general idea is reflected in some of the foregoing citations. Virchow also noticed mysterious minute glistening bodies in endocardial deposits and suppurative foci thrombophlebitic as well as embolic. In puerperal endocarditis, the malignancy of the pyemic process was so much more intense than in simple endocarditis that something special ("etwas Besonderes") surely was at work, and he suggested that if the granules he had seen could be brought into etiologic relation to the endocardial lesion the whole process might be explained.¹⁷ The stage was fully set and waiting for the definitive demonstration of the microbial nature of endocarditis, and this demonstration fell to the lot of Winge and Heiberg.

WINGE'S DEMONSTRATION

In the transactions of the Norwegian Medical Society for 1869 page 78 occurs an untitled report that begins as follows: "E. Winge demonstrated a heart with a peculiar form of endocarditis from a man treated in the Rigshospital for pyemia." This heart (figs 1 and 2) came from a laborer, aged 44, who was taken ill after the tearing out of a corn on the little toe, in the bed of which suppuration developed. Death took place twenty-five days later. The aortic valves presented large grayish vegetations, as did also in more marked form the tricuspid and there were several ulcers with thrombotic deposits on the endocardium of the right side of the heart (figs 1 and 2). There were fresh hemorrhagic infarcts in the left lung and two grayish-yellow infarcts in the left kidney, with softened thrombi in the corresponding arteries. In the endocardial vegetations (Hartnach, ocular 2 immersion lens, objective 9) were leptothrix chains (leptothrixkjeder) which were situated like a rosary or string of beads from the presence of short rods or round granules; in addition, there were many round or rounded bodies, partly bacteria, partly fat granules. Such bodies were found also in the emboli in the renal artery and in small foci in the myocardium, but not in the bed of the corn on the little toe. These bodies were not affected by acetic acid or by potassium hydroxide.

A rabbit was inoculated subcutaneously with material from the heart, but without apparent result. Winge's comments were brief: "It appears to concern a parasitic process; an external focus was present; acute endocarditis is a secondary pyemic process serving as a new focus

¹⁷ Virchow R. Ueber die Chlorose und die damit zusammenhängenden Anomalien im Gefässapparate, insbesondere über Endocarditis puerperalis, Beitr. z. Geburtsh. u. Gynäk. 1: 323 and 354, 1872.



Fig 1—Winge's case 1869, tricuspid endocarditis. I am indebted to Prof Francis Harbitz, of Oslo, for the photographs of this heart.



Fig 2—Winge's case, 1869 the left side of the heart.

for the distribution of microbes." Figure 3 shows that this case was one of streptococcus endocarditis¹⁸

HEIBERG'S CASE¹⁹

This case occurred in a woman, 22 years old following childbirth. There was an ulcerative mitral endocarditis, infarcts in the spleen and kidney, metastatic abscesses in the kidney, and thrombolympangitis in the uterus. The masses in the heart contained numerous fine detritus-like granules between which were rod-shaped bacteria-like bodies and a number of larger and smaller rosary-like chains of granules. These were not attacked by alkalis. No chains were found in the infarcts of the spleen and kidney or in the uterus. The chains were like those described by Winge, but there were not so many bodies. Winge and Heiberg were closely associated and Heiberg gave a full summary of Winge's case. He, also, inoculated rabbits without any result. Small bits of vegetations were placed in the peritoneal cavity and in another experiment an unfiltered suspension of salt solution of the vegetation was given intravenously, death resulting immediately from convulsions.

Against the claim that the microbial invasion might have occurred after death, Heiberg urged that the examinations in both his and Winge's cases were made from twenty-five to thirty hours after death in cold weather and that the bodies were well preserved, in Winge's case frozen stiff. Heiberg also referred to two museum specimens of ulcerative endocarditis in which he could not find any micro-organisms. He finally suggested that ulcerative endocarditis is due to infection from without and is pyemic in nature.

By then clear and simple reports, Winge and Heiberg completed the great work of Virchow and others on acute endocarditis in its relation to infection and pyemia.

Heiberg's description of the microscopic examination in his case reads as follows:

On microscopic examination the thrombus masses on the valvular ulcers and on the chordae show that they consist of numerous fine detritus-like granules,

18 Winge's report in *Förhandlingar i det norske medicinske Selskab* for 1869, p. 78, is not listed in the Index Catalogue, but in the first series, 1884, is listed a review of the report in *Forhandlingar vid det Svenska Lakaresällskapets Sammankomster*, 1870, p. 172. An abstract by Winge himself occurs in *Nord med Arkiv*, 1870, vol. 2, article 14, p. 15. There is a good abstract, entitled *Mycosis Endocardii*, in *Canstatt's Jahresbericht* (295, 1870). And Heiberg's article (*Virchow's Arch f. path. Anat.* 56:407, 1872) also contains the essential details.

19 Heiberg, Hjalmar. Ein Fall von Endocarditis ulcerosa puerperalis mit Pilzbildungen im Herzen (*Mycosis Endocardii*), *Virchow's Arch f. path. Anat.* 56:407, 1872. *Forh. norske med. Selskab*, 1872, p. 60, and 1873, p. 72, *Die Puerperalen und pyämischen Prozesse*, 1873.

between which are numerous more rod-formed bacteria-like bodies and a considerable number of rows of granules arranged in shorter and longer roset-like chains which represent leptothrix chains. There is no distinct fibrin but rather many white blood corpuscles in the thrombus mass. On addition of potassium hydroxide and even on boiling with it the leptothrix chains are not attacked and many of the finer granules also remain although most of them are destroyed by the alkali. In the mitracts observed in the kidney and spleen and the afferent arteries detritus-like granules could be demonstrated but no chains. Nor were any found in the thrombotic lymph vessels on the left margin of the uterus or on the inner surface of the uterus. The chains which in respect to length and

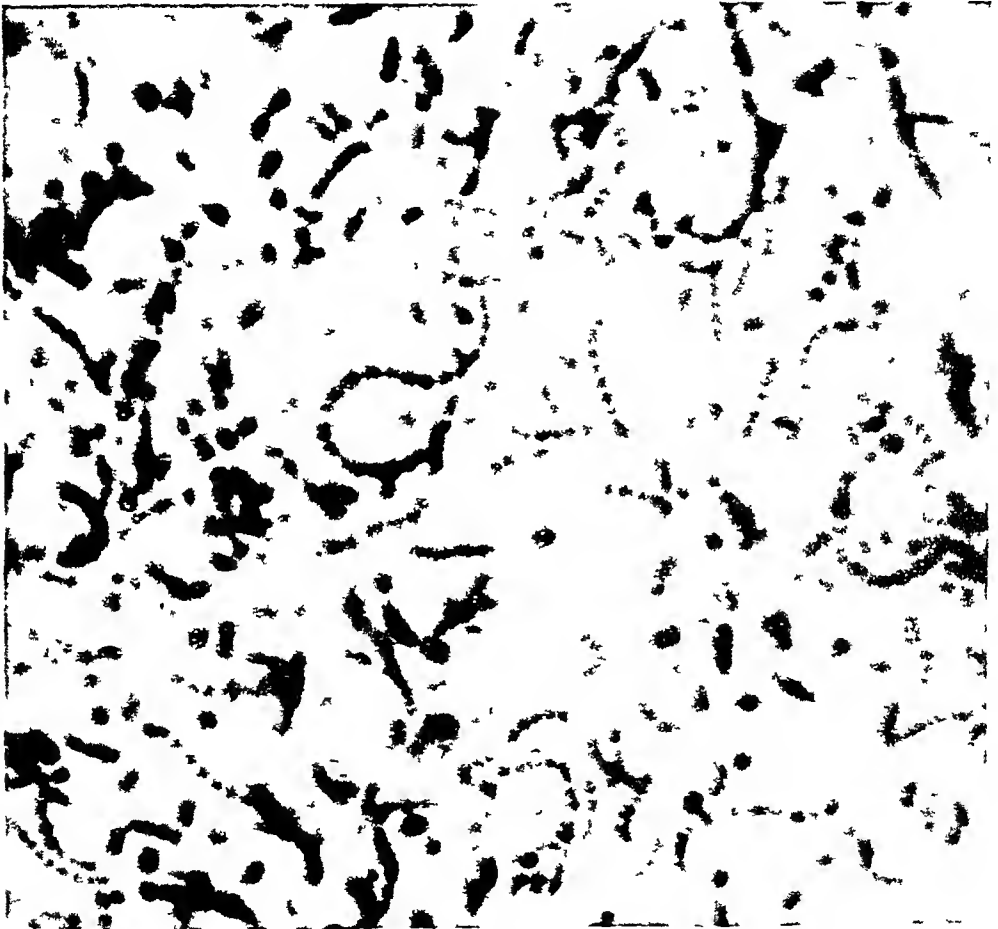


Fig. 3—Photomicrograph of section made by Prof. Francis Harbitz Oslo in 1929 of endocardial vegetation in Winge's case gram stain $\times 2000$. Photomicrograph reproduced by courtesy of George R. Callender Major M.C. U.S.A. Army Medical Museum, Washington D.C.

size of the individual members correspond with those in the heart in Winge's case which is still preserved in the museum here, cannot easily be confused with disintegrating thrombus masses which, of course naturally would be thought of first under the circumstances because of the regularity and the equal size of the granules or members which resist boiling alkali. It is true that occasionally one sees in disintegrating thrombi two three or four definite detritus granules in a row, but the individual granules always vary in size and one never finds—as in the leptothrix chains now described—from ten to twenty connected members

Heiberg's comment on Virchow's work on endocarditis is interesting

On postmortem examination of a young officer, Virchow found numerous vibrios and fungus-like formations in the pulmonary veins, which were regarded as postmortal but the point is that "in the finer cerebral vessels there were found, in addition, numerous colorless cells and here and there similar densely crowded accumulations of very small granules" In Virchow's case of puerperal endocarditis were found peculiar granules set into a somewhat hyaline matrix, "a diphtheritic mass" Virchow assumed "that in the blood itself may be distributed parts of this kind, which multiply in the blood and possess the possibility of striking root on the endocardium and of spreading farther", "that germs are present *intra vitam*, which multiply *post mortem*" The thought of fungi or bacteria must have been before him, but it would be hazardous to conclude from the presence of mere granules that it concerned bacteria or micrococci We would not have concluded that it concerned fungous formations if we had not found granules in chains

According to a note by Virchow at the end of Heiberg's report pieces of both the hearts were sent to him and he found the bodies



Fig. 4—"Vibrios," figured by Vogel in 1846 Virchow said that the small bodies in Winge's case resembled these vibrios

described He questioned whether they should be called "*leptothrixketten*" rather than vibrios The granular mass left after treatment with acetic acid or alkali consisted of dense accumulations of fine granules the parasitic nature of which he did not question He said that in Winge's case, small roundish bodies formed long chains like chains of pearls resembling the vibrios described and illustrated by Vogel (fig. 4) These bodies did not resemble *Leptothrix* Virchow noted that a principal argument for the diagnosis namely, the mobility of the granules and chains, could not be advanced by him because he had before him only alcoholic preparations He went on to say "I know from other experiences how difficult it is to reach a conclusion in regard to such minute bodies and this is also the reason why I expressed myself carefully in my contributions on puerperal endocarditis That it concerns parasitic processes I nevertheless have said definitely and then relation to diphtheritis and to infection of the blood I have expressed in this sense"

EMANUEL WINGE AND HJALMAR HEIBERG

Emanuel Winge 1827-1894 passed his state medical examination in 1851. After a few years in various temporary positions he spent a year of study in Berlin, Prague, Vienna and Paris, giving most of his time to pathologic anatomy and chemistry under Virchow and Hoppe-Seyler. In 1858 he became prosector in the newly established pathologic institute in Oslo (then Christiania) and in the winter of 1858-1859 he again studied pathologic anatomy in Berlin, passing also some time in Holland and England. In the fall of 1859 he accompanied Virchow on a journey in Norway to study leprosy. In 1866 he became professor of pathology, the first such in the Norwegian university, and in 1869 he was appointed professor of internal medicine. While he was professor of pathology his assistant was Hjalmar Heiberg, who succeeded him as professor. Together they studied the preparations on which Winge's report on acute endocarditis is based.

Winge's best published work dates from the period he worked in pathology. In 1863 he published an important article on changes in the internal organs in syphilis. He was an able and conscientious man, painstaking and thorough in his work, greatly respected on all sides, successful and influential in his teaching over a long period in which he emphasized the importance of pathologic anatomy. He has been characterized as 'the pathological anatomist at the bedside'.

Hjalmar Heiberg, 1837-1897 studied pathologic anatomy in Würzburg and Vienna. In 1870 he succeeded Winge as professor of pathology and continued as such until his death. He was a master teacher—'the clinician at the postmortem table'. His remarkably comprehensive grasp of pathologic problems is illustrated in his report on endocarditis and especially in his short monograph on 'Die puerperale und pyämische Prozesse' 1873, which is a pioneer piece of work of fundamental significance in bacterial pathology. It is a classic that deserves to be known better than it is. Here Heiberg said that his attention was led to the relation of bacteria to ulcerative endocarditis and pyemia by Winge's case in 1869. Subsequently he studied a series of such cases, including the case he reported in Virchow's *Archiv* in 1872.¹⁰ His technic was simple indeed: unstained double-knife sections in potassium hydroxide. On page 16 he clearly described what later was included under myocardial segmentation. He made it clear that only a minute lesion of the surface is required for the entrance of bacteria into the body, but whether every case of ulcerative endocarditis results from pyemia cannot be said. He traced the course of the bacteria in certain cases, e. g. puerperal infection through lymph vessels and veins to the heart and from the heart into metastatic foci and finally even into the urinary tubules. He was thoroughly familiar with the literature and referred to Pasteur's and Lister's work as revolu-



E. Winge
Professor i Medicin.

Fig 5—Emanuel Winge (in 1890)

tionizing. He raised the question whether the bacteria are specific and how they are transferred. Is there a spontaneous pyemia? In answer, he stated that ulcerative endocarditis does occur without demonstrable wounds, but in such cases how can infection through the nose, trachea or lungs be excluded? And are not the accessory nasal sinuses danger-



H. Heiberg

Fig. 6—Hjalmar Heiberg

ous possibilities? Finally, let me quote a foreshadowing statement of special interest: "If one considers the properties of protoplasm and the amoeboid cells which often enough wander in between the epithelium from the mucosa, there is a priori nothing in the way of the assumption that even corpuscular elements e. g. bacteria may be taken up by the epithelium and then spread themselves farther in the mucosa and thence along the lymph vessels."

THE INTERVAL BEFORE THE PERIOD OF CULTURAL AND
EXPERIMENTAL METHODS

Immediately following Winge's and Heiberg's reports confirmatory observations began to be recorded. Eberth,⁹ for instance, was practically synchronous with Heiberg in 1872. Eberth described micrococcal masses in the vegetations of acute endocarditis and in pyemic abscesses. From the circumstance that the bacterial masses frequently are loosely deposited without noteworthy valvular involvement he assumed that the bacteria are deposited from the blood and gradually work their way into the valve.

Klebs⁷ and Larsen²⁰, Burkart,²¹ Eisenlohr,²² Fleischhauer,²³ Gerber and Hirschfeld,²⁴ Maier²⁵ and Rosenstein²⁶ described cases in support of and illustrating the view that endocarditis is infectious. Lancereaux in 1873 accepted a puerperal form of endocarditis, but in 1881 he apparently doubted whether the facts at hand were sufficient to establish the parasitic nature of acute endocarditis as claimed by Winge and Heiberg. Others, like Hillel, denied offhand that acute endocarditis could be infectious. Many of these reports have good illustrations.

In 1876 Rosenstein²⁶ wrote as follows: "In a small but well attested series of cases these substances ('granular masses') have been proved with certainty to consist of parasitic organisms of the micrococcus genus (Winge, Heiberg, Burkardt, Eisenlohr)."'

In 1878, Koester²⁷ on the basis of recorded observations and his own concluded that acute endocarditis is a micrococcal and embolic process and itself a depot for further embolic processes. He pointed out that in all cases, except Winge's, the bacteria observed in acute endocarditis were described as micrococci, micrococcal colonies, micrococcal masses, etc., and that such forms undoubtedly had been seen by Rokitsansky (1855) and by Virchow (1856). Rokitsansky⁵ saw finely

20 Larsen. Om ondartet Endokardit, Norsk Mag. f. Laegevidensk. **3** 279, 1873.

21 Burkart. Ein Fall von Pilzembolie, Berl. klin. Wchnschr. **11** 149, 1874.

22 Eisenlohr, C. Ein Fall von ulcerativer Endocarditis mit Micrococcus-embolien, Berl. klin. Wchnschr. **11** 389, 1874.

23 Fleischhauer, J. Akuter Gelenkrheumatismus mit multiplen miliaren Abscessen, Virchows Arch. f. path. Anat. **62** 386, 1875.

24 Gerber and Birch-Hirschfeld. Ueber einen Fall von Endocarditis ulcerosa und das Vorkommen von Bakterien in dieser Krankheit, Arch. d. Heilkunde **17** 208, 1876.

25 Maier, R. Ein Fall von primärer Endocarditis diphtheritica, Virchows Arch. f. path. Anat. **62** 145, 1875.

26 Rosenstein, S. S. Encyclopaedia of the Practice of Medicine, edited by H. von Ziemssen. American editor, Albert H. Buck, 1876, vol. 6, p. 66.

27 Koester, K. Embolische Endocarditis, Virchows Arch. f. path. Anat. **72** 257, 1878.

granular masses the nature of which he did not specify and Virchow referred to similar structures and their possible parasitic nature

In this country, it was several years before the significance of the new views of acute endocarditis was noticed. Except for the statement in von Ziemssen's "Encyclopedia" ²⁴ the first mention of the new departure appears to have been in 1878 when Keating ²⁵ in describing a case of ulcerative endocarditis with pyemia, cited Lancereaux (1873) as quoting the observations of Winge and Heiberg verified in one case by Virchow in which "vibriones of filiform shape were found in the ulcers." "If the germ theory be accepted the emboli may be charged with bacteria," he said.

In 1879 Loomis ²⁶ reported to the New York Pathological Society that he had found bacteria in the lesions in a case of pyemia. A discussion followed on the question "whether the bacteria found were the cause or the effect of the pathological changes but as no conclusion was arrived at, the society went into executive session." In 1880 Peabody ³⁰ in the same society spoke of finding micrococcal masses in the vegetations the valve substance and the renal vessels in ulcerative endocarditis. The following year Osler ³¹ showed the society microscopic preparations from endocardial vegetations containing minute bodies corresponding to bacteria and resisting acids alkalis ether and chloroform. In the discussion Alonzo Clark and Satterthwaite denied that these bodies had any pathogenic significance. Clark raised the question how such bodies could enter from without, and Satterthwaite held that they had entered after death, and Osler himself seemed to be inclined to view them as concomitants rather than the real *materia morbi*.

In 1881, Garland ³² reported an instance of ulcerative aortic endocarditis in the yellowish-white deposit of which were small white specks "composed of minute round bodies (micrococci)." He gave probably the best American review of this period on infectious endocarditis.

The nature of ulcerative endocarditis has long been the subject of discussion and experimentation. Virchow detected, many years ago a difference between this and ordinary endocarditis. Seeking an explanation of this difference, he cut

²⁸ Keating M & S Reporter **39** 206, 1878 Tr Coll Phys Philadelphia **4** 27, 1879

²⁹ Loomis M Rec **17** 42 1880

³⁰ Peabody G L M Rec **18** 131, 1880 Bull New York Path Soc **1** 207, 1881

³¹ Osler, William Infectious (So-Called Ulcerative) Endocarditis, Arch Med **5** 53 1881, On Some Points in the Etiology and Pathology of Ulcerative Endocarditis, Tr Internat M Cong **1** 341, 1881 Ulcerative Endocarditis, M Rec **19** 245 1881

³² Garland G M Ulcerative Endocarditis Boston M & S J **104** 434, 1881

up various substances and injected them into the veins of an animal. Bits of caoutchouc simply produced the ordinary results of mechanical obstruction to the circulation, while animal substances (bits of muscle, fibrin, etc.) caused severe inflammation, suppuration and sloughing. Virchow therefore concluded that the phenomena of infection were due to chemical changes in the emboli. Others followed this idea in assuming that the irritant effects are due to the decomposition of the emboli which plug the vessels. Lancereaux thought the poisoning was caused by an alteration in the connective tissue of the valves themselves, and not by disintegration of the vegetations alone. Virchow noticed that the valvular deposits contained fine closely packed granules, which were insoluble in potash, acetic and hydrochloric acids but were dissolved in chloroform. He considered them to be of a fatty nature.

Professor Winge was the first one (1869) to advance the theory that these granules are living organisms, and he called the disease *mycosis endocardii*. This same view was taken by Professor Heiberg, of Christiania, who sent specimens to Virchow for examination. With further study Virchow, Klebs, Koster, and a number of other Germans have given their approval to this theory and they say that the organisms found are micrococci, vibriones, bacteria, and leptothrix filaments. Some of these observers believe that the germs are the essence of the disease. Heiberg inclines to the germ side of the question but he allows that cases of ulcerative endocarditis present themselves wherein no parasites can be detected. Eberth thinks that the bacteria are introduced into the blood from without and become aggregated into a sticky mass which adheres to the surface of the cardiac valves. Here they multiply rapidly and dropping off, are distributed to all parts of the body. On the other hand, some writers repudiate the germ theory with great vigor and claim that the parasites, if present, are merely the accidents of the disease. Hiller says that bacteria and leptothrix are constantly present in the healthy mouth and if they are so dangerous we ought to be poisoned all the time. He thinks the granules described are merely detritus.

Osler wrote on acute endocarditis several times first in 1881. In his first contributions¹ he is rather disappointing largely because he was not fully familiar with the literature of the previous decade. He found what he thought were micrococci in all the cases that he examined. In his Gulstonian lectures² on malignant endocarditis in 1885 he was fully abreast with his time and urged the study of cultures from the vegetations, particularly in so-called simple endocarditis and that consideration be given to the possibility of the experimental production of endocarditis. In 1908 he wrote "The infective character of endocarditis has only been fully recognized since the studies of Winge, Koster and Heiberg."³

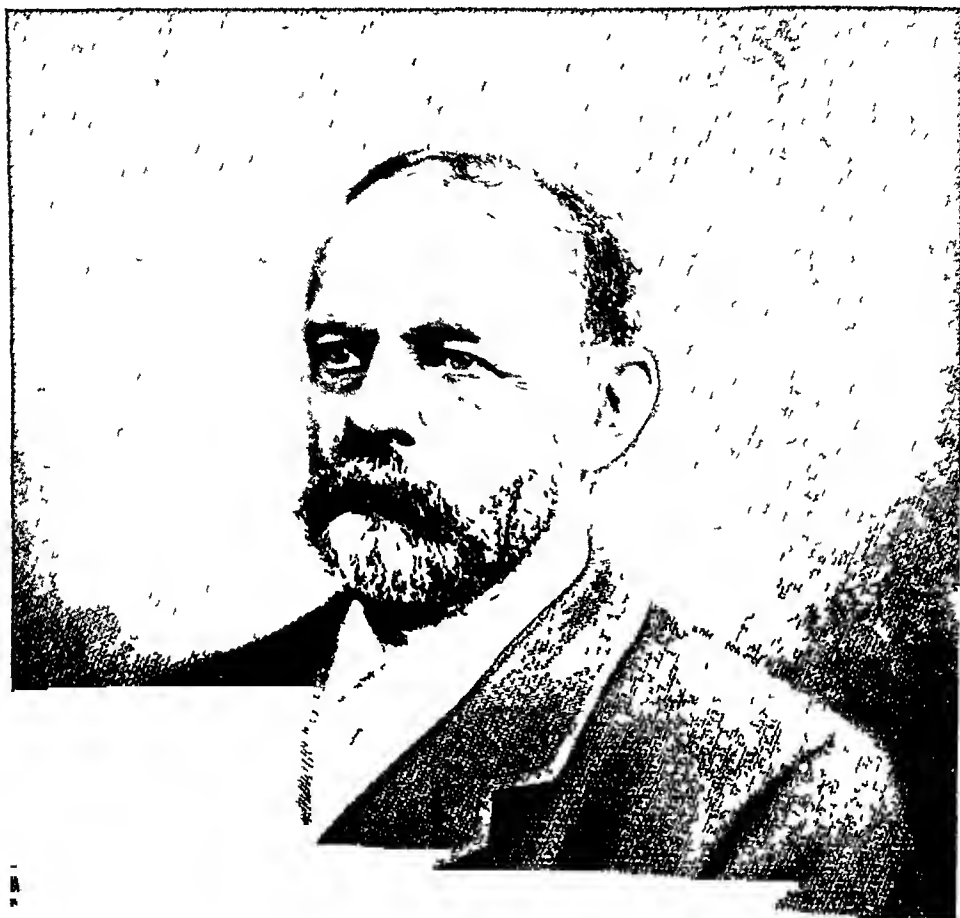
In 1879 Park⁴ then in Chicago pointed out that in ulcerative or diphtheritic endocarditis micrococci form a prominent element, embolic

33 Osler William. The Gulstonian Lectures on Malignant Endocarditis. Brit M J 1:467 1885.

34 Osler William. Acute Endocarditis in Osler and McCrae. Modern Medicine ed 1 Philadelphia Lea & Febiger 1908 vol 4 p 133.

35 Park Roswell. A Conspectus of Three Different Forms of Acute Inflammatory Cardiac Disorder. Chicago M J & Examiner 39:349 1879.

infarctions with consequent abscesses frequently develop, the emboli acting as "infective excitants." In the vegetative or subacute form of endocarditis, on the other hand, micrococci are not found, the action of emboli in such cases being mechanical and not infectious.



Christian Fenger

Fig 7—Christian Fenger, 1840–1902

From this review it is evident that Fenger's demonstration before the Chicago Pathological Society fifty years ago is worthy of special recognition as a pioneer demonstration in this country of the infectious origin of acute endocarditis.¹

The next phase in the development of the knowledge of acute endocarditis is the study of its causative bacteria by cultural methods and of

its experimental production I shall not go into this phase, except to mention Prudden's³⁶ work on experimental endocarditis mainly because of his comprehensive grasp of the work with which we have been dealing. Winge, he said, formulated for the first time a consistent theory of acute endocarditis, based on careful observation and the assumption that microbes may be transported from external foci through the veins to the heart, where they produce the lesions by lodgment on the valves

36 Prudden, T. M. An Experimental Study of Mycotic or Malignant Ulcerative Endocarditis, *Am J M Sc* **93** 55, 1887

THE INTRACELLULAR "SYMBIONTS" AND THE "RICKETTSIAE"

R W GLASER, D Sc
PRINCETON, N J

(Concluded from p 96)

THE "RICKETTSIAE"

The intracellular micro-organisms of arachnids and insects have interesting pathologic affinities through the various so-called "rickettsiae"

The problems of the "rickettsiae" received an impetus during the World War, when insects, especially lice, played such an important rôle in the transmission of disease and in the production of epidemics among the troops of the various nations. Since the war, the interest in the subject has abated somewhat, however, many workers have continued to contribute valuable information and have extended the work not only in man, but in domestic animals and in invertebrates.

The genus *Rickettsia* was erected by da Rocha-Lima in 1916 for certain minute micro-organisms found in the human body louse (*Pediculus humanus*) infected with the virus of exanthematic typhus fever. These micro-organisms had been seen previously by Hegler and by von Prowazek, but the generic name was chosen to honor Howard Taylor Ricketts, a martyr to the investigations of typhus fever pursued in Mexico City in 1910. Some writers believe that Ricketts first observed members of this group, but without completely interpreting their significance. Da Rocha-Lima designated the species "*prowazeki*" to aid in perpetuating the memory of von Prowazek, the capable investigator, also sacrificed in the work on typhus fever. Since 1916, *Rickettsia prowazeki* has become the type species for all subsequent researches on a group of micro-organisms segregated from established classifications.

Topfer (1916) found a form of rickettsia, *R. wolhynica* (*R. quintana*), in body lice collected from soldiers afflicted with trench fever. Some observers, for example, Bacot (1921) and Wolbach, Todd and Palfrey (1922), thought this form the same as *Rickettsia pediculi*, which Munk and da Rocha-Lima (1917) considered a nonpathogenic normal parasite of lice. Sikora (1921) seems to have further established the probability, however, that *Rickettsia pediculi* is a separate species from *R. wolhynica* (*R. quintana*).

In 1917 and 1919, Wolbach greatly extended the work of Ricketts on Rocky Mountain spotted fever. Wolbach found an interesting

and extremely pleomorphic micro-organism invariably associated with the disease. It is highly probable that Ricketts observed one of the forms in which the parasite reveals itself, but was unable to bring order out of the confusing facts that the problem presents. Wolbach, however, felt that the various forms found were genetically related and merely represented different stages of an extremely pleomorphic rickettsia. This author erected a new genus and named the Rocky Mountain spotted fever parasite *Deimacentoicoccus rickettsi*, the generic name being derived from the disease transmitter discovered by Ricketts, namely, the wood tick *Deimacentoicoccus venustus* (andersoni).

In 1923, Sellards reported the discovery of another form of rickettsia in Japan, which he felt was associated with the "Japanese flood fever," tsutsu-gamushi disease, transmitted by the bites of infected mites, *Trombicula akamushi*. Sellards named the micro-organism *Rickettsia nipponica*.

The fifth pathogenic rickettsia described to date is *Rickettsia immunantum*, discovered by Cowdry in 1925. This micro-organism, according to Cowdry, is the cause of a serious condition, heart-water disease, in sheep, goats and cattle in South Africa and is transmitted by a tick, *Amblyomma hebraeum*.

Recently, Sellards and Siler (1928), while working on dengue fever in Manila, found rickettsiae in infected specimens of the transmitter of mosquito disease, *Aedes argentus* (*aegypti*). These writers were extremely conservative, however, from their work, it seems likely that a causal relationship exists between the micro-organisms found and the disease.⁷

The foregoing enumeration to date comprises the entire list of diseases due to so-called rickettsiae transmitted to man and the higher animals. Much more work, however, has been accomplished with various arachnids and insects in determining the distribution of supposedly nonpathogenic rickettsiae among them, their introduction into and localization within the invertebrate host and their differentiation from the pathogenic forms. Aside from any biologic interest that such work may present, it is important also from the medical point of view, because, as is well known, many arachnids and insects are either actually or potentially capable of transmitting parasites and infectious diseases.

⁷ Megaw and Rao (1928) showed that in many places in India sporadic typhus-like fevers occur of which the vectors are entirely unknown. Most of these fevers strongly suggest transmission by an arthropod from a rodent reservoir, and the authors consider it desirable that these diseases be investigated with special reference to ticks, mites and other forms. They also think it perfectly possible that a typhus virus might be conveyed by two alternative arthropods, especially by the louse and the tick.

The most extensive general surveys for rickettsiae in arthropods were those made by Cowdry (1923, 1925) and by Heitig and Wolbach (1924). Other workers, such as Noller (1917, 1920), Sikora (1918, 1921), Aikwright, Atkin and Bacot (1921) and Noguchi (1926), have also contributed. In all, between thirty and forty different forms of rickettsiae have been described as occurring in such a variety of forms as mites, ticks, *Mallophaga* (biting lice), *Siphunculata* (sucking lice), bedbugs, beetles, sandflies, mosquitoes, house flies, pupipara (keds) and fleas.

Woodcock (1922, 1923) thought that all rickettsiae in human and mammalian tissues and in insects were cell granules, artefacts or debris. Other investigators considered the pathogenic and non-pathogenic rickettsiae small micro-organisms distinct from bacteria. Da Rocha-Lima (1916), Jungmann (1916) and Sikora (1918) thought that they were closely related to the "strongyloplasmata" of Lipschutz and to the "chlamydozoa" of von Prowazek (Sikora, 1921). However this may be, Cowdry's recast definition, of 1926, is probably accepted at present by many workers. This author defines the rickettsiae as "Gram-negative, bacterium-like organisms of small size, usually less than half a micron in diameter, which are found intracellularly in arthropods, which may be more or less pleomorphic and stain rather lightly with aniline dyes, but which resemble in most of their properties the type species, *Rickettsia prowazeki*."

The coccoidal forms of *Rickettsia* may measure less than half a micron in diameter (*R. prowazeki*, *R. wolhynica*, *R. munnantium*). The spherical forms of *R. melophagi* of the sheep ked measure from 0.4 to 0.6 microns in diameter, and the rods from 0.3 to 0.4 microns in width by from 0.5 to 0.6 microns in length. The bacillary form of *Deimacanthionus rickettsi* is larger, measuring from 0.5 to 1 micron in length, whereas the filamentous forms of the rickettsia of the bedbug (*R. lectularia*) may attain a length of from 3 to 8 microns. The type species (*R. prowazeki*) and some others are smaller than most bacteria, but, as shown, the minute size usually emphasized has exceptions.

The rickettsiae often occur as cocci or diplococci, as lanceolated or short and longer straight and curved bacillary forms and filamentous species, especially within the invertebrate host. The various forms are often arranged in pairs, end to end, and frequently one finds a longer form paired with a shorter or bud form. In general, the rickettsiae described are extremely pleomorphic, but it seems probable that some structures observed are not always genetically related. One need merely recall the interesting monosymbiotic, dysymbiotic and trisymbiotic relationships that exist in many insects. This possible confusion is difficult to avoid, however, until more of the micro-organisms, under considera-

tion, have been isolated and studied in pure cultures. Notwithstanding, good evidence appears to exist in favor of cases of extreme pleomorphism within a single species.

Much has been made of the staining reactions of the rickettsiae as a character that permits a segregation from bacteria. Many rickettsiae stain less intensely than the majority of bacteria, and their outlines are not as sharp. Some stain well only when Giemsa's method is applied. All the described rickettsiae are gram-negative, and most of them are nonacid-fast. How much one can rely on tinctorial reactions in order to separate one group of micro-organisms from another is difficult to say. I should like to offer the suggestion that in the case of the smaller rickettsiae, the delicacy with which they stain, in contrast with most bacteria, is possibly only apparent rather than real due to the difference in size. A small stained body is likely to be a less effective light screen than a larger one. Some bacterial groups are gram-negative, some gram-positive. The characterization of the group as gram-negative has also exceptions in the rickettsiae (bacterioids, symbionts) of the roaches (*Blattidae*).

The rickettsiae are usually considered nonmotile micro-organisms. However, Buchner (1922) and Heitig and Wolbach (1924) found the filamentous forms in the bedbug definitely motile after Arkwright, Atkin and Bacot (1921) had stated that no motile forms existed. I have examined a number of bedbugs recently, and am convinced that the filaments in the malpighian tubes and in the mycetome are motile.

The rickettsiae within the arthropod host may be extracellular or intracellular and in one case were also intranuclear. They often occur in groups within or on the surface of cells and form masses, producing what has been called the typical picture of "rickettsiae." Some rickettsiae are widely distributed throughout the host, others are restricted to certain tissues. In the ticks infected with Rocky Mountain spotted fever, the micro-organism has intranuclear, intracytoplasmic and extracellular phases, but multiplication occurs only while it is intracytoplasmic and intranuclear. Sometimes, the parasite appears to be restrained, but it may occur within all parts of the alimentary canal, ducts of the salivary glands, all parts of the reproductive system in both sexes, the brain and nerve trunks and the muscles. In short, nearly all the tissues of the tick may become infected with *Dermacentor* *rickettsi*.

All bedbugs throughout the world are infected with the non-pathogenic *Rickettsia lectulana*, which is present within a mycetome, but according to various writers is also found within the intestine malpighian tubes, organ of Beilese ovaries and testes. It has also been found in the blood and produces a general infection. Multiplication, however, occurs entirely intracellularly.

Rickettsia prowazeki in the infected human louse multiplies within the intestinal epithelial cells, and is restricted to these and to the lumen of the alimentary tract. *Rickettsia ruminantium*, in ticks infected with heart-water disease, behaves in much the same manner. Similar events occur in *Melophagus ovinus*, every specimen taken throughout the world being infected with the nonpathogenic *Rickettsia melophagi*. *Rickettsia wolhynica* (*R. quintana*), in the infected human louse, is entirely extracellular, it occurs and multiplies in enormous numbers within the intestinal lumen and on the surface of the epithelial cells.

Other cases might be cited, but enough has been said to show that the rickettsiae usually occur and multiply intracellularly, but may also occur and multiply extracellularly.

Systemic or cellular reactions do not often occur in arthropods infected with rickettsiae. Wolbach (1919) found no cellular reaction in the tick against *Deimacentorixenus*. The intranuclear forms completely fill the nucleus, but the host does not appear affected. Arkwright, Atkin and Bacot (1921) found that the rickettsiae of the bedbug multiplied to such an extent within the malpighian tubules that certain cells are distended to more than twice their normal diameter. Cowdry (1925) also found no injury of the tissue in sixteen species of ticks other than mechanical distention of certain cells by the parasites. On the other hand, several observers noticed that *Rickettsia prowazeki* often kills lice by excessive multiplication within the intestinal lumen. In these cases, the parasites are said to interfere with the louse's digestion. Barukin, Zakharov, Kompaneetz and Barukina (1927) stated that typhus infection in the louse frequently causes a rupture of the epithelium of the intestinal wall, followed by the death of the insect. This may represent a case of reversion or of incomplete adaptation to the host. In general, however, perfect adaptation exists and no serious injury results, even in cases such as that in the spotted fever tick and the bedbug, in which the invertebrate hosts appear to be overwhelmed with parasites.

The question of complete and incomplete adaptation between parasite and host is further strikingly illustrated in the manner in which various arthropods become infected with rickettsiae. The most perfect adaptation exists in those forms in which transmission through the ovum from generation to generation has been established. This manner of infection occurs in most of the species that have been thoroughly investigated. Cowdry in his studies on ticks found that the rickettsiae of all species studied by him are located within the eggs and are transferred to succeeding generations. The rickettsia of the bedbug was found within the ovaries and eggs by Arkwright, Atkin and Bacot and by Hertig and Wolbach. The latter authors also observed a representative of this group of micro-organisms within the ovaries and eggs of

the mosquito, *Culex pipiens*. Noller found the ova of *Melophagus ovinus* (sheep ked) infected with *Rickettsia melophagi*. In 1923, this author and Kuchling demonstrated the same parasite within the blood of sheep, so it seems likely that the insect may become infected in two ways. Wolbach found that *Dermacentorixenus rickettsi* is transmitted through the ova of the wood ticks infected with spotted fever. This fact was demonstrated experimentally by inoculating guinea-pigs with emulsions of the eggs. Wolbach also found this rickettsia within spermatozoa, but whether transmission to succeeding generations is effected through the male tick is not known. Ricketts long ago had observed another rodlike form present in large numbers in the ovaries and egg cells of the wood tick. Wolbach also found the same form in all the ticks associated with spotted fever, infected and noninfected. He considered it entirely distinct from the micro-organism associated with the disease and found that it was likewise transmitted through the egg. Noguchi (1926) found this micro-organism in the ovaries and eggs of the spotted fever tick and concluded that it was extremely difficult to differentiate the nonpathogenic rickettsia-like organism from *Dermacentorixenus rickettsi*.

Rickettsia prowazeki, *R. wolhymica* (*R. quintana*) and *R. munnantium* represent cases of imperfect adaptation to the arthropod vectors.⁸ The first two are not transmitted to succeeding generations of human lice and the last one is also not so transmitted by the tick *Amblyomma hebraeum*. These vectors become infected only when they feed on the blood of diseased subjects. In the case of the heart-water tick, however, Cowdry found another form distinct from *Rickettsia munnantium*, nonpathogenic and more bacterium-like, which is transmitted to succeeding generations through the eggs.

The work on the transmission of the rickettsiae from generation to generation is still in its beginnings. The embryologic phase of the subject has scarcely been touched and until the ova and oviposited eggs have been sectioned and carefully studied it will remain doubtful whether or not more than one species of parasite is involved. This suggestion is worth considering in those cases in which the parasites reveal themselves as extremely pleomorphic forms. Attempts to obtain cultures would, of course, be preferable to a study of sectional material, but obtaining cultures is more difficult and is less likely, at present to guarantee immediate results. The literature on the intracellular symbionts found in insects abounds in cases of invasions by one, two or three micro-organisms, which usually segregate during the

⁸ This imperfection is due either to losses of adaptive characters or to the fact that the rickettsiae are still in the process of adaptation to the invertebrates. I incline to the former view for reasons to be divulged later.

embryologic development of the host, follow separate channels of infection and often settle within specific tissues and organs. It must further be recalled that both Cowdry and Wolbach actually found two types within the hosts investigated by them, and, further, Noguchi (1926) had difficulty in differentiating a pathogenic from a non-pathogenic form within the same host.

The micro-organisms under consideration are usually specific for the host. The same species of rickettsiae rarely inhabits two species of invertebrates. Maver (1911) experimentally transmitted Rocky Mountain spotted fever by using three ticks, namely, *Deimacentor marginatus*, *Deimacentor variabilis* and *Amblyomma americanum*, but whether natural infection ever occurs in any manner other than through the bite of the spotted fever tick is questionable. Fletcher, Lesslar and Lewthwaite (1928), however, showed that *Trombicula deliensis* is the normal mite carrier of the tsutsugamushi virus in Sumatra and in the Malay States, while *Trombicula akamushi* transmits the disease in Japan and in Formosa.

On the other hand, more than one parasite frequently infects a single host species, and thus often makes a differentiation extremely difficult, if not impossible. The human body louse may harbor *Rickettsia prowazekii* or *Rickettsia wolhymca* (*R. quintana*) and perhaps also *Rickettsia pediculi*. The spotted fever ticks at times harbor *Deimacentoraxenus rickettsi* and besides are always infected with *Bacillus rickettsiformis* (Noguchi [1926]). The heart-water ticks may be infected with *Rickettsia ruminantium*, but invariably harbor another form. When a nonpathogenic rickettsia is encountered, it always occurs in every individual of the specific host throughout the world.

The rickettsiae that have been tested for their resistance to physical and chemical agents show nothing characteristic that would distinguish them from bacteria and certain other micro-organisms.

Some of the diseases caused by the rickettsiae have been classified with the filterable viruses from time to time. However, Olitsky (1917, 1922) found that the typhus fever virus does not pass through Berkefeld candles grades "V" and "N". Ricketts (1907), Spencer and Parker (1924) and Spencer (1925) found that the virus of spotted fever behaves in a similar manner. Strong, nevertheless, in 1918, was able to pass the virus of trench fever through a Chamberland "L" filter when it was maintained at a pressure of 760 mm of mercury. Knuth and du Toit (1921) classed the infective agent of heart-water disease among the filterable viruses. Theiler, however, according to Cowdry (1926), believed that this virus would not pass through Berkefeld and Chamberland filters. The filtrates used in the aforementioned experiments were not microscopically examined for rickettsiae, but were tested pathogenically for living virus. No experiments in filtra-

tion have been performed with any of the rickettsiae exclusively parasitic in arachnids and insects. It is possible that some rickettsiae under stated conditions might pass through a certain type of filter.

The artificial cultivation of the rickettsiae has been beset with many difficulties perhaps primarily because they represent a highly specialized group of parasites exacting in their requirements. The isolation of any member of this group in pure culture is highly desirable so that an insight into its true taxonomic position and biology may be obtained. Many of the species apparently nonpathogenic to man and higher animals are highly specialized and parasitic in the invertebrate host. The culture of any one of these might in an unexpected manner lead to the cultivation of a pathogenic form, which, in turn, might yield a prophylactic vaccine or a curative serum.

Weigl (1920) gave normal lice of the human body (*Pediculus humanus*) intrarectal injections of leukocytes from typhus fever patients and from infected guinea-pigs. By so doing, he obtained a growth of *R. prowazeki* in the intestinal tract of the lice. This result was confirmed by Bacot and Segal (1920) and by Arkwright and Bacot (1923). Wolbach and Schlesinger (1923) found that the virus of typhus fever survived in tissue plasma cultures for a length of time corresponding to the survival of endothelial cells, and that the virus multiplied in these cultures. Transplants to fresh tissue cultures were successful. Coccoid bacillary and filamentous forms appeared in the cultures thus exactly duplicating the morphology of *R. prowazeki* as described for lice infected with typhus. In a similar manner, Wolbach, Pinkerton and Schlesinger (1922) and Wolbach and Schlesinger (1923) cultivated *Deimacentrionus rickettsi*. In this case, a filamentous form appeared in the cultures in addition to the forms already described for the arachnid and mammalian hosts infected with the virus of Rocky Mountain spotted fever.

Sellards (1923) reported the cultivation of *R. nipponica* on "chocolate" blood agar, but Nagayo's work (1924) threw some doubt on the causal relationship between this micro-organism and the "Japanese flood fever."

Sikora in 1921 cultivated the nonpathogenic *R. pediculi* from lice of the human body in a unique manner. In order to obtain an overabundance of vigorous multiplying forms, she injected concentrated suspensions of *R. pediculi* into the body cavity of lice with extremely fine glass capillary pipets. Previous to this, however, to overcome the antagonism of the phagocytes, she first filled these by injecting the lice with carmine, dead bacteria or blood cells. Under these conditions the rickettsiae multiplied vigorously within the body of the lice. When the multiplying rickettsiae were then transferred to human blood agar and maintained for twenty days at a temperature of 37 C., round,

flat, grayish-white colonies, the size of pinheads, began to appear. These colonies clung so tightly to the mediums that they were only removed with difficulty. Such cultures showed tremendous number of rickettsiae with many swollen and dead forms. Better initial growths were obtained when the blood agar was inactivated for one half hour at 57 C. Sikora, however, was unable to obtain further transfers of her cultures.

In 1917, Noller cultivated a *citithidium* from the middle intestine of the sheep ked, *Melophagus ovinus*, on especially prepared semisolid blood agar plates. The blood used in this medium had previously been inactivated. In these cultures, Noller also discovered a tiny coccobacillus, which was later found occurring plentifully in the intestine of every sheep ked. Noller thought that this small micro-organism showed a striking morphologic similarity to *Rickettsia prowazeki*, the supposed cause of typhus fever, and for this reason named it *Rickettsia melophagi*. This tiny micro-organism is a short bipolar rod, which, as stated, occurs free in the intestinal lumen of the sheep ked and also within the intestinal epithelial cells. By taking advantage of differences in susceptibility to temperature between the citithidium and the rickettsia, Noller was able to separate the two forms. On plates held at 29 C, minute, pinpoint, transparent colonies of the micro-organisms began to appear in from ten to fifteen days and many colonies appeared only after forty days. The maximal diameter of these colonies varied between 0.4 and 0.6 mm. When inoculated plates were held at a temperature of 22 C, they remained sterile.

Jungmann, in 1918, further investigated *Rickettsia melophagi* and found that it was a gram-negative, nonacid-fast and nonmotile form, greatly resembling *R. prowazeki* and *R. wolhynica*. He verified Noller's experiments in cultivation, and by using Noller's medium obtained growths on slants, as well as on plates, but more rapidly when sheep blood instead of horse blood had been added. Jungmann, moreover, maintained his cultures for several months by transplanting frequently. Cultures attempted in liquid or on routine laboratory mediums invariably remained sterile. Variations of size and form were common, all gradations from coccoid and ovoid shapes to rods were observed, and chains of three or four units were seen. This writer was unable to find *Rickettsia melophagi* in sheep blood, but Noller and Kuchling, in 1923, found that the micro-organism existed in the blood of sheep and could there be culturally demonstrated. Jungmann discovered a second method of transmission to the ked by observing that the insect's ova become infected during an early stage. This fact was verified by Heitig and Wolbach in 1924. Jungmann emphasized this fundamental difference between the rickettsia of the sheep ked and *Rickettsia*

provascki and *R. wolhymca*, neither of which is transmitted from generation to generation. *Rickettsia melophagi* is a normal and regular inhabitant of the intestine of the sheep ked owing to the establishment of hereditary transmission, *Rickettsia provascki* and *R. wolhymca*, as previously stated, gain access to the human louse only with infected human blood during the biting process. Further, the form found in the sheep louse does not appear to be pathogenic in laboratory animals, and lastly it can be cultivated on artificial mediums, a feat not yet accomplished for the two forms pathogenic in man. Hertig and Wolbach also succeeded in cultivating Noller's sheep ked rickettsia, but were unable to obtain the continuous growth of the colonies during long periods as described by Noller. The colonies of Hertig and Wolbach remained at a barely visible size. These writers found that *Rickettsia melophagi* in cultures behaves like a bacterium and that the organism under these conditions is slightly longer and more definitely rodlike than when in the sheep ked.

Amigstein (1927) isolated five strains of *Rickettsia melophagi*, which he carefully studied morphologically, culturally and serologically. He showed that certain slight differences exist between the strains, but that they correspond to the forms that are found in vivo within the ked and are all closely related. From his work, Amigstein felt that the rickettsiae should not be classified separately, that, on the contrary, they are closely related to the *Corynebacteria* (diphtheroids). He further stated that the rickettsiae are extremely pleomorphic and easily adaptable, and that the so-called rickettsia type is only one of several appearances.

Noguchi (1926) found that the spotted fever tick *Deimacentor venustus* (andersoni), in some instances, revealed several types of micro-organisms morphologically resembling the inciting agent of spotted fever. This investigator cultivated three species from ticks at room temperature on special mediums, but the most consistently grown was a form that he named *Bacillus rickettsiformis*. He had difficulty in obtaining initial growths, but found that a gradual adaptation occurred and that finally less specialized mediums could be employed. The three micro-organisms proved nonpathogenic for guinea-pigs, rabbits and *Macacus rhesus*. In morphologic features, they resemble the forms found in smears and sections of ticks, yet their presence has no relation to the infectivity of the tick infected with the virus of spotted fever. Immunologically, also the three types are not related to the virus of spotted fever. The three micro-organisms are pleomorphic under cultural conditions, and Noguchi consequently raised the question whether or not the nonpathogenic minute forms of the rickettsia and the somewhat coarser forms found in the tick are morphologic variants caused by differences in nutrition, oxygen tension, tissue reactions, etc.,

in the different tissues and cells in which the parasites are embedded. Noguchi concluded his work by stating "At all events the differentiation of the nonpathogenic rickettsia-like organisms from *Deimacentocecus rickettsi* is extremely difficult."

It can finally be stated that *Rickettsia melophagi* from the sheep ked can be properly adapted to artificial mediums. The experiments of Noller were amply verified by Jungmann, Hertig and Wolbach and Amgstein. It is also highly probable that Sellards cultivated *Rickettsia nipponica* from mites and that Noguchi grew three rickettsia-like micro-organisms from the tick *Deimacentor venustus*. Probably none of the forms pathogenic in higher animals have been adapted to artificial mediums. The experiments of Weigl and of Wolbach and Schlesinger, however, constitute definite advances.

COMMENT

A comparison of the section on the intracellular "symbionts" with that on the "rickettsiae" will show that many of the problems are identical and others overlap. Mites, ticks and insects are exceedingly old creatures and the intracellular symbionts are, as was shown, well adapted to their hosts. Many rickettsiae are also well adapted to their invertebrates, others are not so well adapted. Some workers believe that the virus of Rocky Mountain spotted fever is in the process of adaptation to the tick. It is generally distributed throughout the body and is transmitted through the egg, but not all ticks of the species are infected. In other words, the association appears rather recent. If this line of reasoning is followed in the case of typhus fever, trench fever and heart-water disease, the association of the former two with the louse and of the latter with the tick is to be considered still more recent, because transmission from generation to generation has as yet not been established at all, and the parasites are entirely restricted to the arthropod intestine and to its epithelial layer. In general, it is safer, however, to regard the association as having originated among the invertebrates in the form of disease, because they are phylogenetically older than the vertebrates. On the basis of this conclusion, it is best to assume that some of the intracellular "symbionts" or "rickettsiae" are in the process of adaptation to the higher animals, in which several of them now produce maladies. *Rickettsia melophagi* according to this assumption represents a parasite still perfectly adapted to the sheep ked that only recently began to invade the blood of sheep, where it at present maintains itself without doing any harm. It is perfectly conceivable that this parasite may follow the course adopted by the typhus and the heart-water parasites in other words, may gradually lose its still perfect adaptation to the invertebrate host and assume

parasitic tendencies in sheep.⁹ Many other "symbionts" or "rickettsiae" found in blood-feeding insects, but not yet found in vertebrates, probably have latent parasitic potentialities. This point of view has analogies elsewhere. Most protozoologists believe that the various forms of the hemosporidia of malaria were anopheline parasites before they became pathogenic in birds and in man.

Summing the matter up in another way one may state that evidence exists for the assumption that the class of micro-organisms discussed are still in the process of a pronounced evolution, and that certain branches may ultimately culminate in a whole series of new and unsuspected diseases among the higher animals. This assumption may be worth a consideration by those who claim that all new diseases arise through mutations of etiologic agents instead of through apparently slower and more orderly processes.

Although this review could not concern itself with the microscopic phases of the diseases due to the rickettsiae in higher animals, it should be mentioned in conclusion that the parasites do not change their habits much after invasion of the vertebrate hosts. Within these, they are all also primarily intracellular parasites. *Rickettsia ruminantium* probably occurs throughout the body of goats, sheep and cattle, but is prevalent in the renal glomeruli and in the capillaries of the cerebral cortex. It is, however, a typical endothelial parasite, restricted in distribution to the endothelial cells of the smaller blood vessels and portions of them that break off into the blood stream. In Rocky Mountain spotted fever and in typhus fever, a specificity for the endothelium of the peripheral blood vessels also exists. This localization of the pathogenic rickettsiae within the blood system of vertebrates proved ideal for the establishment and maintenance of the arthropod vector relationship.

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⁹ I realize that this view is unorthodox. It is usually held that when a parasite invades vertebrates, it either is destroyed or multiplies to such an extent that injury to the host follows. According to this prevalent view, a harmless parasite found maintaining itself in vertebrates indicates a terminal stage in its parasitic activities. However a gradual loss of characters adaptive to the invertebrate accompanied by a gradual adaptation to the higher animals, terminating in true parasitism, appeals more strongly in these specific cases after due consideration of various general views on the subject.

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Notes and News

University News, Appointments, Promotions, Resignations—On his retirement from the professorship of pathology and bacteriology in Tufts College Medical School, Boston, Timothy Leary was honored at a complimentary dinner.

Max Cutler has assumed charge of the New York City Cancer Institute.

Everett S. Sanderson is now in charge of the department of pathology and bacteriology in the school of medicine of the University of Mississippi.

Edmund V. Cowdry, professor of cytology, Washington University, St. Louis, will study parasitic diseases in East Africa at the request of the British government.

Theobald Smith and James Ewing have accepted appointments as consultants in bacteriology and in pathology, respectively, to the division of laboratories and research of the State Department of Health at Albany, New York.

In Berlin, B. Fraenkel has been placed in charge of the medicolegal institute, pending selection of a permanent successor to F. Strassmann, the former director.

Jefferson H. Clark has been appointed director of the laboratory of the Philadelphia General Hospital.

Barton W. Johnson has been appointed pathologist and radiologist at the General Hospital, Mansfield, Ohio, to take the place of Samuel H. Richman, who has accepted a like position in the Sherman Hospital, Elgin, Ill.

Kenneth Goodner has been appointed instructor in bacteriology and immunology in the school of public health at Harvard University.

Henry H. Plowden has been appointed director of the pathologic laboratory of the Columbia Hospital, Columbia, S. C.

In the school of medicine of the University of Illinois, Lloyd Arnold has been made professor of bacteriology and preventive medicine, I. Pilot, associate professor of pathology and medicine, and R. J. Kremer, instructor in pathology and bacteriology.

Ella Sachs Plotz Foundation—During the past year, twenty-four grants were made, most of them to investigators outside of the United States. The amounts granted varied from \$250 to \$1,000. Seven of the investigations aided relate to the general topic of nephritis. During the six years of its existence, the Foundation has made ninety-five grants. Applications for grants for 1930-1931 must be made before May 1, 1930. Address: Dr. Joseph C. Aub, 695 Huntington Avenue, Boston.

Grant for Study of Trachoma—The Commonwealth Fund of New York has made a grant of \$50,000 toward the investigation, during a period of five years of trachoma and other infectious diseases of the eye at the Department of Ophthalmology of the Washington University School of Medicine.

Grant for Study of Undulant Fever—The Commonwealth Fund of New York has made a grant of \$18,800 to the National Research Council in Washington, D. C., toward a three year program of research on problems of undulant fever at the Central Brucella Station, Michigan State College, East Lansing, Mich., under the auspices of the Council's committee on infectious abortion.

Philadelphia Pathological Society—The recently elected officers of the society are Baldwin Lucke, president, V. H. Moon, vice-president, and Isolde T. Zeckwer, secretary-treasurer.

British Medical Association—At the annual meeting of the association in Winnipeg, Canada, Aug. 25-29, 1930, there will be a joint section on pathology, bacteriology, physiology and biochemistry of which Robert Muir will be the president and G. Hadfield (Royal Free Hospital, Gray's Inn Road, W. C. 1, London) the secretary.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

STUDIES ON SEX (INTERSTITIAL CELLS IN GIGANTISM) WILLIAM G. DOWNS, JR., *Am J Path* 5 295, 1929

The case presented here, a definite giant, did not have the hypoplastic genitalia or the marked feminine secondary sex characteristics usually associated with such a condition. Microscopically there was an apparently complete absence of testicular interstitial cells, which, while they are supposed to limit bone growth, are likewise supposed to produce, in part at least, the masculine type of secondary sex characteristics.

AUTHOR'S SUMMARY

THE EFFECT OF POTASSIUM IODIDE, THYROID EXTRACT AND ANTERIOR PITUITARY EXTRACT UPON REGENERATION AND EARLY COMPENSATORY HYPERTROPHY OF THE THYROID GLAND S. H. GRAY, *Am J Path* 5 415, 1929

Regeneration of thyroid tissue after an incision occurs rapidly in control and potassium iodide-fed animals. Regeneration is delayed by the feeding of pituitary extract and thyroid extract. Early compensatory hypertrophy is markedly inhibited by pituitary extract and thyroid extract but only slightly by potassium iodide. The possible causes of a slight diminution in the average hypertrophy in the potassium iodide series which was observed at early periods are discussed. Compensatory hypertrophy may appear as early as eight days following the removal of parts of the thyroid gland.

AUTHOR'S SUMMARY

AUTOTRANSPLANTATION AND HOMOIOTRANSPLANTATION OF CROSS-STRIATED MUSCLE TISSUE IN THE RAT JULIUS ELSON, *Am J Path* 5 425, 1929

After autotransplantation of striated muscle tissue in the rat, well preserved muscle tissue was found as late as 118 days after transplantation, the further fate of the muscle tissue has not yet been studied. After homoiotransplantation there is less regeneration of the muscle tissue in the first period after transplantation, and much more degeneration due to invasion by lymphocytes and, to a less extent, by connective tissue at subsequent periods. As a result of these conditions, homoiotransplanted muscle disappears much earlier than autotransplanted muscle, no preserved tissue being present at fifty days. It is therefore probable that in addition to the action of the lymphocytes, the homoiotoxins may injure the muscle tissue directly, diminishing the regenerative process and increasing the subsequent degeneration. Nowhere is there seen a true outgrowth of muscle fibers, either in continuity with the preformed transplanted muscle or by budding. The old muscle tissue, after a primary degeneration of its major portion, undergoes regenerative processes, consisting in an increase of its sarcoplasm and a proliferation of its nuclei, subsequently there is a differentiation of the sarcoplasm into typical striated muscle, in which cross-striations are again formed. In the course of time the nuclear proliferation becomes less active, the nuclei decrease in number and become situated peripherally within the fibers, while the fibers as such increase in size until there are almost normal muscle fibers. This process of growth is, in certain respects, comparable to compensatory hypertrophy or hyperplasia rather than to regeneration in the strict sense.

AUTHOR'S SUMMARY

VASODEPRESSOR SUBSTANCES IN THE LIVER AFTER OBSTRUCTION OF THE COMMON DUCT I. S. RAVDIN, *Arch Surg* 18 2191, 1929

Surgeons have observed that patients recently operated on for relief of obstruction of the common bile duct frequently went into severe shock. The syndrome

became known as "liver shock." It nearly always occurs several hours after the surgical procedure and recovery from the anesthetic. It may occur after mere drainage of the gall bladder. The author conducted experiments inquiring into the origin of this condition. He produced experimental obstruction of the common duct in dogs and after certain intervals the liver was removed and extracts made of it. The extracts were sterilized and were injected into other animals, chiefly cats. It was demonstrated that there was an excess of vasodepressor substances in the jaundiced liver, and this excess may be the cause of the clinical shocklike state. The mechanism might be interpreted as being due to the sudden release of pressure on the portal system, so that these substances find their way into the blood stream. Both histamine and choline were found in excess in the jaundiced livers.

N ENZER

PERFRINGENS ANTITOXIN AND EXPERIMENTAL INTESTINAL OBSTRUCTION J C OWING and C A McINTOSH, Arch Surg **18** 2237, 1929

The authors conducted several experiments in an effort to determine the inhibitory effect of *Bacillus perfringens* antitoxin on the toxins accumulating in intestinal obstruction, and also experiments to determine the relative toxicity of *B. perfringens* toxin as compared with those occurring in intestinal obstruction. They found that the *B. perfringens* antitoxin had no effect on dogs with obstruction of the upper portion of the small intestines. Also, in those experiments in which they attempted to neutralize the toxins in the isolated intestinal loops with the antitoxin of *B. perfringens*, no success was obtained. In other words, the material in the intestinal loops was just as toxic after the addition of the antitoxin. Dogs immunized against the toxin of *B. perfringens* were just as susceptible to lethal doses of intestinal obstruction toxin. The postmortem observations on dogs dying after the intravenous injection of *B. perfringens* toxin as compared with those dying after the injection of loop toxin showed that there was a greater amount of hemolysis in the former.

N ENZER

RELATIVE EFFECTS OF DISTENTION ON DIFFERENT PORTIONS OF THE INTESTINE C A DRAGSTEDT, V F LANG and R F MILLET, Arch Surg **18** 2257, 1929

This is an experimental study in an effort to determine the effects of distention of the intestine on its own circulation, and also the changes produced by such distention in different portions of the intestinal tract. The experiments were done by injecting air, nitrous oxide gas and mineral oil into the intestinal tract as a whole and into isolated loops. Briefly stated, the effect of this distention on the circulation was more severe in the proximal portion than in the terminal portion, it was greatest in the duodenum and least in the rectum. The effect on the circulation is stasis with resulting pallor and anemia, and finally complete cessation with resulting interference with the nutrition of the wall of the intestine. The duodenum is particularly susceptible to very low pressures. With relatively small increases, varying degrees of damage from cyanosis to infarction may be produced. Anatomically, there would appear to be some explanation for this in that the blood vessels pierce the muscularis in the small intestine at the mesenteric margin, whereas in the large intestine they enter further and further away from the mesenteric border, and come closer to the antimesenteric border. Hence the blood vessels are more superficial in the distal portions of the intestinal tract, and withstand pressure better.

N ENZER

A COMPARISON OF THE MANNER OF EXCRETION OF NEUTRAL RED AND PHENOL BY THE FROG'S KIDNEY JEAN OLIVER and ESHREF SHEVKY, J Exper Med **50** 15, 1929

Phenol red and neutral red are excreted by the perfused frog's kidney by different routes. Phenol red is excreted chiefly through the glomerulus, neutral

red through the tubules. Some slight excretion of each of these dyes by the converse mechanism is possible, though there is no evidence in our experiments that necessitates such a conclusion. The importance of methods leading to the production of a normal volume of urine by the perfused kidney is emphasized.

AUTHORS' SUMMARY

STUDIES OF TISSUE MAINTENANCE. PEYTON ROUS and H. P. GILDING, *J. Exper. Med.* **50** 189, 1929.

The spread of various highly diffusible dyes through the living animal has been utilized as an indicator of the ability of the circulation to serve the tissues under various conditions. The method is direct and searching. Blood service to the viscera, as demonstrated by it, is normally far more profuse than to the skin and muscles, for evident physiologic reasons. After hemorrhages which greatly reduce the blood bulk, service to the viscera is in general still well maintained even though the animal be in extremis. However great the compensatory contraction of the splanchnic vessels may be—and physiologists have long supposed it to be very great—it does not suffice to hinder blood service anywhere in the digestive tract. On the other hand the service to certain unessential abdominal organs (spleen, omentum, urinary bladder) is cut off in large part or wholly, and in comparison with the essential viscera, the skin and most of the skeletal muscles of the bled animal are largely deprived of circulation. This neglect takes a curious form, some regions being still fairly served by the blood while others next them are no longer ministered to. In the skin the areas served, or not served, are highly irregular but are to some extent determined in situation by local pressure factors. Within the muscles the neglect is orderly in arrangement and is largely referable to compensatory vasoconstriction. Certain of the muscles, those used in respiration and in swallowing, furnish significant exceptions to the general rule, being excellently served despite the serious general state. The red bone marrow of the depleted organism continues to be well served by the blood even though situated in limbs that are, for the rest, almost devoid of a circulation. The pregnant uterus also is excellently maintained despite the serious general state. The changes are such as would tend to conserve the forces of the depleted organism and to contribute to its recovery.

AUTHORS' SUMMARY

STUDIES OF TISSUE MAINTENANCE (THE LIVER AND DIGESTIVE TRACT AFTER HEMORRHAGE). H. P. GILDING, *J. Exper. Med.* **50** 213, 1929.

The vascular readjustments in compensation for a greatly reduced blood bulk affect the service rendered by the blood to the gastro-intestinal tract and liver far less than they do that to the skin and muscles. Into these latter tissues, India ink is carried almost not at all, whereas it circulates in quantity through the capillaries of the bowel and liver. Evidently vasoconstriction is much less effective in these viscera. Nowhere in them does one find a patchy ischemia like that so widespread in the peripheral tissues. Blood service is maintained to the same extent everywhere throughout the liver even when one of its two sources (hepatic artery or portal vein) is obstructed, and the intrahepatic blood pressure is brought very low. A pronounced patchy ischemia of the stomach and large bowel can be induced by intravenous injection into normal animals, of sufficient epinephrine to cause the systemic blood pressure to mount to an abnormally high level. Solution of pituitary used in the same way has a greater effect, blood service to the organs mentioned may be completely abolished by means of it. In both instances, though, service to the small intestine and liver is still excellently and evenly maintained.

AUTHOR'S SUMMARY

HORMONES OF THE FEMALE REPRODUCTIVE CYCLE. E. C. DODDS and F. DICKENS, *J. Obst. & Gynaec. Brit. Emp.* **36** 92, 1929.

This is a critical review in which the attempt is made to correlate the main facts on which most workers are agreed.

A. J. KOBAK

BERIBERI AS AN EDEMA DISEASE J MEIBIUS, Virchow's f path Anat **271** 432, 1929

In four autopsies on patients with beriberi the longitudinal striation of the heart muscle fibers was very distinct while the cross striation was indistinct. There was little intercellular edema, and fatty change was mostly absent. The indistinctness of the transverse striation shows that the normal differences in the water contents of the isotropic and the anisotropic parts of the muscle fiber have disappeared. Since the shifting of fluid from one part into the other is the main factor in muscle contraction (Engelmann), the fatal deficiency of heart muscle function is explained by these observations of indistinct transverse striation. The author explains this and other edematous lesions in beriberi as directly caused by the deficiency in vitamin B. There is no reason to explain the muscle lesions as secondary to nerve lesions. All of the principal symptoms of beriberi can be explained on the basis of muscle lesions.

ALFRED PLAUT

Pathologic Anatomy

NECROSES OF THE LIVER IN MALARIA OSCAR KIOTZ, Am J Trop Med **9** 241, 1929

Twelve cases of acute malignant malaria were studied in which the parasites (*Paramecium falciparum*) were demonstrated during life. The necroses in the liver at necropsy are described. Similar necroses were found in one case of blackwater fever. The case was one of malarial (*P. falciparum*) blackwater fever. Two other fatal cases failed to show changes although the blood showed large numbers of subtertian parasites.

JOHN PHAIR

EXPERIMENTAL STUDY OF ACQUIRED RESISTANCE OF THE RABBIT'S RENAL EPITHELIUM TO MERCURIC CHLORIDE WARREN C HUNTER, Ann Int Med **2** 796, 1929

Having previously demonstrated that rabbit's renal epithelium possesses a high degree of resistance to the injurious effects of uranium, Hunter undertook to determine whether or not the renal parenchyma was capable of developing an acquired immunity for mercuric chloride. The minimum lethal dose of sublimate was first determined by subcutaneous and intravenous injections. Immunization experiments were then carried out, starting with small quantities of sublimate and gradually increasing the dosage. Local corrosive action and irregularity of absorption after subcutaneous administration, the danger of thrombosis following intravenous injection, and the excretion in the intestine with the development of a severe enterocolitis, render mercuric chloride an undesirable substance to use for accurate determination of acquired immunity of renal epithelium. Owing to differences in absorption of the sublimate, several injections may be given without producing any demonstrable changes in the renal epithelium, while in other animals the same quantity will produce well marked chronic glomerulotubular nephritis. A slight degree of acquired immunity for sublimate can be demonstrated in regenerated epithelium and glomeruli. A constant observation in the sublimate kidney is the envelopment of necrotic cells by regenerating epithelium.

WALTER M SIMPSON

A CASE OF MULTIPLE MYELOMA WITH BENCE-JONES PROTEIN IN THE PLEURAL EFFUSION E E MARCOVICI, Ann Int Med **2** 881, 1929

Marcovici presents the clinical details of a case of multiple myeloma, presumably involving only the ribs, in which Bence-Jones protein was found in the fluid aspirated from the thoracic cavity before it could be demonstrated in the urine.

WALTER M SIMPSON

HEMATOLOGIC STUDY OF THREE GENERATIONS OF A WHITE FAMILY SHOWING ELLIPTICAL ERYTHROCYTES W C HUNTER and R B ADAMS, Ann Int Med 2 1162, 1929

The erythrocytes of one male parent, all of his eight children, and three of his grandchildren showed elliptical morphology. After studying sealed fresh preparations of blood over long intervals and exposing the cells to carbon dioxide, the authors conclude that this morphologic abnormality is not of the type seen in sickle cell anemia. Several of the subjects showed some degree of anemia.

WALTER M SIMPSON

BRONCHOGENIC SQUAMOUS CELL CARCINOMA RALPH G MILLS and NOLIE MUMFORD, Arch Int Med 43 516, 1929

A detailed report is given of a case in which there was reason to suspect infection with *Endameba histolytica*, but which proved to be a bronchogenic carcinoma associated with hydrothorax, mucoid infiltration of the lung and disease of the gallbladder and kidney.

Certain cells, when observed on the warm stage, manifested activity and assumed morphologic forms that might readily lead to confusion with amebas.

Cells of the human body, especially histiocytes, under pathologic conditions simulated amebas when viewed in sections stained either with hematoxylin and eosin or with iron hematoxylin.

One case does not justify sweeping conclusions, but the intensive study of this case involved extensive search of the literature and was made against a background of many years of work in parasitology. Therefore, it is safe to conclude that if there is doubt as to a given cell in the body being an ameba, it probably is not. Disregard of this criterion may lead to further erroneous conclusions.

AUTHORS' SUMMARY

ENCEPHALITIS PERIARIALIS DIFFUSA WALTER D SCHELDEN, JOHN B DOYLE and JAMES W KERNOHAN, Arch Neurol & Psychiat 21 1270, 1929

A clinical and pathologic report of two cases of so-called Schilder's disease is made by Schelden and his co-workers.

In both cases the macroscopic changes were characteristic of Schilder's disease: large areas of degeneration of the subcortex, absence of involvement of the gray matter of the cortex or only of its deeper layers. The degeneration in this disease usually starts in the occipital, but may also start in the frontal lobe.

Microscopic changes were early breaking up of the myelin, followed by that of the axons which generally suffer less severely, both the myelin and axons break up into smaller fragments and become finally transformed into lipoids which are taken up by scavenger cells (gitter cells). The glia shows marked progressive changes, especially in the form of proliferation of astrocytes and the appearance of large numbers of giant cytoplasmic cells ("gemastete") glia cells. It is remarkable that the type of glia cells known as oligodendroglia showed in these cases regressive changes in the form of so-called swollen oligodendroglia. A wall of hyperplastic astrocytes was seen between the degenerated and the normal tissues. Microglia was abundant and satellitosis was present in the advanced stages. So-called mucocytes, that is, cells containing mucus, were absent but were present within the perivascular spaces. These contained masses of scavenger cells mixed with lymphocytes, few polymorphonuclear cells but no plasma cells. It is evident that in contrast to the gross pathologic changes, the microscopic picture of Schilder's disease shows nothing specific, nor is the clinical picture characteristic. However, in the first patient, a boy aged 7 years, the diagnosis has been made before the patient's death, from the following symptoms: apathy, change of personality, rapid onset of blindness and deafness, bulbar symptoms with signs of involvement of the motor and sensory neurons and frequent convulsions. The course was rapid. The patient died four months after the onset. Previous diseases were various.

infectious diseases of childhood and preceding the onset there was a bilateral otitis media

In the second case, the patient was a woman, aged 27 Six and one-half weeks prior to admission to the hospital she had been delivered of her first child by forceps, two and a half weeks later visual disturbances set in—blurring of vision followed by complete blindness within one week, later, facial weakness developed with weakness and partial paralysis of the left side of the body, generalized tremor, involuntary evacuations and coma Death followed two months after onset Here the actual condition was not recognized and an abscess of the brain was considered probable A craniotomy was done but no abscess was found

G B HASSIN

EPENDYMOMAS EDGAR F FINCHER, JR, and GAYLORD P COON, Arch Neurol & Psychiat 22 19, 1929

Fincher and Coon state that tumors of ependymal origin are rare In an analytic study of 140 gliomas eight were found to be tumors of cells of ependymal derivation The largest number have been located in the posterior fossa in close proximity to the fourth ventricle Ependymomas are slowly growing tumors They tend, according to Bailey and Cushing, to extend down the spinal cord In this they differ from medulloblastomas, which seldom do so They are very cellular, the nuclei being spherical or oval, the cell body is coarsely granular and polygonal Some cells are ependymal spongioblasts When these predominate they encircle the blood vessels from which they are separated by a clear zone In suitably stained specimens this is filled with the processes of the embryonic cells They contain so-called blepharoplasts—minute, deeply staining granules surrounded by clear halos within their cytoplasm

In the eight cases studied, the majority of the ependymomas were situated in the cerebrum close to the lateral ventricles, whereas this type of glioma is most commonly found in the posterior fossa

Grossly the tumors were reddish gray, encapsulated, lobulated and moderately firm On the surface of the majority of these tumors were cysts varying in size from 1 to 4 cm, containing thin yellow fluid which did not coagulate (in two cases it was removed on exposure to the air) In this respect the fluid strikingly differed from that found in other glomatous cysts The presence of ependymal spongioblasts, when stained with Hortege's silver carbonate methods, is of great diagnostic value Some tumors had centers of calcareous deposits which were distinct enough to show in x-ray pictures

In two cases (6 and 7) incomplete removal of the tumor was accomplished No return of the symptoms was noted after a lapse of fourteen and thirteen months, respectively The ependymomas of the cerebrum generally offer a favorable prognosis

G B HASSIN

PYRAMIDOPALLIDAL DEGENERATION SYNDROME DUE TO MULTIPLE SCLEROSIS J M NIELSEN, D C WILSON and R R DIETERLE, Arch Neurol & Psychiat 22 45 1929

In a man, aged 50, symptoms indicative of a typical pyramidal lesion of the lower extremities (weakness, spasticity, exaggerated tendon reflexes, absent abdominal reflex, Babinski and similar signs) were associated with signs and symptoms (tremor, parkinsonian attitude) of an extrapyramidal lesion of the upper extremities, chin and head Many other symptoms were present, such as parosmia, scotomas, mild sensory and bladder disturbances There was a remission of one or two years' duration The course was atypical, the majority of symptoms began first on one side, and then affected the other, while the ordinary classic signs of multiple sclerosis (ocular symptoms, speech, intention tremor) were absent A diagnosis of multiple sclerosis was considered, but was rejected Necropsy, however, revealed this condition The authors conclude that a combined pyramidal and

extrapyramidal lesion may be produced not only by arteriosclerosis, lesion of the basal ganglia and epidemic encephalitis but also by multiple sclerosis

G B HASSIN

THE HISTOGENESIS OF VON RECKLINGHAUSEN'S DISEASE S H GRAY, Arch Neurol & Psychiat **22** 91, 1929

In two typical cases of von Recklinghausen's disease, sarcomatous changes took place. In one of these cases Gray studied serially several small tumors which were attached to the phrenic and intercostal nerves. The sections included some parts of the uninvolved nerve contiguous to the small tumors. He illustrates his views and conclusions with ten photographs and photomicrographs. His conclusions are that "there can be no question" that in his two cases of von Recklinghausen's disease, a relationship between the cells of the sheath of Schwann and those comprising the tumors does not exist, that the tumor arose not from the embryonic cells of Schwann, as advocated by Verocay, but from the perineural connective tissue. Such a view, he maintains, is supported by the character of the tumor cells themselves and especially by the character and metastatic formation of the sarcomatous nodules.

G B HASSIN

STUDIES ON INFLAMMATION VALA MENKIN, J Exper Med **50** 171, 1929

Trypan blue injected into normal subcutaneous tissue passes rapidly to the regional lymphatic node and is found in lymph drawn from its efferent lymphatic. When the dye is injected into the normal peritoneal cavity it rapidly appears in the lymph of the retrosternal lymphatics and stains deeply the retrosternal lymphatic nodes. Trypan blue injected into the site of inflammation in the subcutaneous tissue or in the peritoneal cavity is fixed in the inflamed area and fails to reach the regional lymphatic nodes. If an inflammatory reaction has been produced in the dermis or in the subcutaneous tissue, trypan blue injected into the circulating blood enters the site of inflammation and is fixed so that the tissues are deeply stained.

AUTHOR'S SUMMARY

THE EFFECT OF UNILATERAL NEPHRECTOMY ON THE TOTAL NUMBER OF OPEN GLOMERULI IN THE RABBIT ROBERT A MOORE and GREGORY F LUKIANOFF, J Exper Med **50** 227, 1929

Under the experimental conditions employed, from 44 to 78 per cent of the glomeruli of the normal rabbit kidney contain circulating blood at any one moment. After unilateral nephrectomy, the number of glomeruli in the remaining kidney which contain circulating blood is increased to 91 to 99 per cent. Compensation for the removal of one kidney is accomplished during the first ten days at least, by an increase of the number of open glomeruli in the opposite kidney.

AUTHORS' SUMMARY

THE LESIONS IN THE SKELETAL MUSCLES IN EXPERIMENTAL SCORBUTUS GILBERT DALLDORF, J Exper Med **50** 293, 1929

Muscle degeneration was constantly found in the intercostal muscles of scorbutic guinea-pigs. It has likewise been found in the masseter and diaphragmatic muscles. Exercise will produce an identical lesion in other skeletal muscles in scorbutic animals. The lesions appear to be an intrinsic part of the scorbutic process. It is suggested that the tenderness over muscles in scorbutic animals and in man may be due to this myopathy.

AUTHOR'S SUMMARY

IRREGULAR UTERINE HEMORRHAGE WILFRED SHAW, J Obst & Gynae Brit Emp **36** 1, 1929

Shaw's paper is based on a thorough study of 200 consecutive cases of irregular uterine hemorrhage (exclusive of obvious causes such as tumors and diseases of

adjacent organs) in which the endometrium and in many of the cases the uterus and ovaries likewise were available for study. It is shown that the terms "endometritis" and "metritis" are too loosely used and that the inflammatory processes are only assumptions. Shaw finds these conditions rather rare, and when present resemble the inflammatory processes found in other organs. Involution of the puerperal uterus was studied by means of Weigert van Gieson stain. Shaw disagrees with Goodall's original conception that the involuting vessel is replaced by a newer vessel growing into the lumen of the old one. During puerperium a subendothelial proliferation, or swelling, and a granular atrophy of the muscle fibers take place in the arteries. The veins and placental sinuses undergo similar processes in involution. Hyaline degeneration of the media takes place which through swelling and distortion, reduces the caliber of the vessel. The subendothelium also swells. Elastic tissue is deposited around the blood vessels and between the muscle bundles. This tissue increases with each pregnancy. The deposit of elastic tissue around the veins and in the media and external elastic lamina of the arteries may give the impression of a new vessel forming within the older one. During subinvolution the formation of elastic tissue appears to be retarded. Some connective tissue is also laid down around the vessels and between the muscle bundles. No cases were noted in which a large amount of elastic tissue was associated with irregular uterine hemorrhage and no condition was found in the menstruating women in which the muscle cells are replaced by fibrous tissue. Shaw concludes, therefore, that neither subinvolution nor a fibrotic state of the uterus are underlying factors in causing irregular uterine hemorrhage. A large group of cases having irregular uterine hemorrhage are associated with ovarian dysfunctions in which the full development of the corpus luteum is inhibited and the follicle becomes cystic. In these cases the endometrium is hyperplastic, the glands cystically dilated and the superficial surface necrotic. Another group of menstrual disorders occur when the ovaries are shrunken and have hemorrhagic follicles projecting over their surfaces. The endometrium in these cases is hyperemic and edematous. Other cases of menstrual disturbances not as definite in character nor as numerous as those in the aforementioned two groups are also found to be associated with disease of the ovaries. Shaw prefers to consider all cases of irregular uterine hemorrhage that are not secondary to obvious disease of the endometrium under the heading of metropathia.

A. J. KOBAK

A LARGE FATTY TUMOR OF THE UTERUS JOHN WEBSTER BRIDE, J. Obst. & Gynaec. Brit. Emp. 36 83 1929

A 9 pound (4 Kg.) oval tumor of the uterus which was removed under the impression that it was a fibromyoma is reported because of its rarity. The patient was a multipara aged 63, whose chief complaint was severe vaginal bleeding occurring after the menopause. The author conceives this tumor to have originated from a large fibroid.

A. J. KOBAK

LIPOMA OF FALLOPIAN TUBE SAMPOERNO, Ztschr. f. Gynäk. 53 1123, 1929

Benign nonepithelial tumors of the fallopian tube are rare. The first lipoma was apparently reported in 1921 since that time two others have been recorded. The one reported by the author occurred in a woman aged 52, and was a chance finding in the adnexa of a uterus removed for carcinoma. The tumor was situated near the fimbriated end. The fimbriae and ostium were normal. The nodule was about the size of a cherry, sharply delimited and encapsulated. Its lipomatous character was evident in the gross. Microscopically it was composed of adipose tissue, which was subdivided by strands of fibrous tissue. The tumor was subserous as was the case in the first lipoma to be recorded, whereas the remaining two were submucous and polypoid.

O. T. SCHULTZ

FIBROMYOMA OF FALLOPIAN TUBE A W HOCHLOFF, *Ztschr f Gynak* **53**
1125, 1929

Dietrich, in 1926, was able to collect thirty-eight cases of fibromyoma of the fallopian tube. The example recorded by Hochloff occurred in a woman, aged 35, who had complained of periodic attacks of pain in the right inguinal region for ten years. The pain bore no relation to menstruation. The last previous attack of pain before admission had lasted three days. A mass the size of an apple could be palpated to the right of the uterus. The preoperative diagnosis was cyst of the ovary. At operation the proximal portion of the right tube, which formed the pedicle of the tumor mass, was found twisted on itself. The tumor, which was attached to the ampullary portion of the tube, measured 7 by 5 by 6 cm and weighed 285 Gm. It was composed of smooth muscle and fibrous tissue and was somewhat edematous from partial strangulation. There was no sharp delimitation between the muscle of the tube wall and that of the tumor. Most of the previously recorded fibromyomas have arisen from the interstitial portion of the tube, only one other case of ampullary tumor being noted by Dietrich. The largest previously reported fibromyoma of the tube weighed 3,000 Gm.

O T SCHULTZ

HEMORRHAGES OF THE LARGE ARTERIES IN CARCINOMA OF THE ESOPHAGUS
AND STOMACH AND FUSOSPIROCHAETAL INFECTION K WOLKOFF and
W D ZINSERLING, *Ztschr f Krebsforsch* **28** 449, 1929

In six cases of hemorrhage of the large arteries occurring in association with carcinoma of the esophagus or stomach, the vascular rupture was found to be caused not by tumor infiltration, but by gangrene caused by infection with associated fusiform bacilli and spirochetes.

H E EGGERS

Pathologic Chemistry and Physics

ENDOGENOUS URIC ACID AND HEMATOPOIESIS J KRAFKA, JR, *J Biol Chem*
83 409, 1929

The endogenous uric acid may arise from the extruded nuclei of the normoblasts on the maturation of the erythrocytes. More than 29 cc of red corpuscles are produced daily, in the normal man, together with about 29 Gm of extruded nuclear material. The uric acid equivalent of the latter is 4.23 Gm, a quantity many times larger than that excreted during maintenance on a purine-free diet. The output of endogenous uric acid is greatly increased following severe hemorrhage, reaching a maximum on the second day, just preceding the period of marked reticulocyte increase.

ARTHUR LOCKE

THE STORAGE OF MANGANESE AND COPPER IN THE ANIMAL BODY AND ITS
INFLUENCE ON HEMOGLOBIN BUILDING R W TITUS and J S HUGHES,
J Biol Chem **83** 463, 1929

Both manganese and copper may be essential supplements to iron in the vital synthesis of hemoglobin.

ARTHUR LOCKE

BIOMETRY OF CALCIUM, INORGANIC PHOSPHORUS, CHOLESTEROL, AND LECITHIN
IN THE BLOOD OF RABBITS. EFFECTS OF A MALIGNANT TUMOR ALVIN R
HARNES, *J Exper Med* **50** 109, 1929

Experiments are reported in which it was shown that the calcium, inorganic phosphorus, cholesterol and lecithin in the blood of normal rabbits were influenced by inoculation with a malignant tumor. Animals in which death was due to tumor gave results on which the following conclusions are based. A marked increase in inorganic phosphorus of blood serum and cholesterol of whole blood followed inoculation. The ratios of cholesterol to calcium and lecithin to calcium increased

in trend, while the calcium to inorganic phosphorus, lecithin to cholesterol, and lecithin to inorganic phosphorus ratios showed a marked decrease in trend. The cholesterol-lecithin were all negative.

AUTHOR'S SUMMARY

THE ION CONTENT OF GASTRIC FLUID E SCHAIRER, Klin Wchnschr 8 1113, 1929

The human gastric fluids contain appreciable amounts of K which calculated as Cl is approximately 11.4 per cent of the total chloride, and is not changed much during secretion in the same person. With increasing acid secretion the Na content of the gastric fluids diminishes, and in hypo-acidity or anacidity it is proportionately markedly increased, the K content unchanged, and consequently the ratio Na to K is altered in favor of the Na. In hypo-acidity and normal acidity the neutral salt content in contrast to the MCl content is not appreciably diminished.

AUTHOR'S SUMMARY

THE FERMENT ACTIVITY OF MUSCLE TISSUE FROM A MUMMY OF 3,000 YEARS AGE E SEHRT, Klin Wchnschr 8 1177, 1929

The macroscopic oxidase reaction with muscle tissue from a mummy of 3,000 years age was strongly positive.

AUTHOR'S SUMMARY

THE ELECTROLYTE CONTENT OF SERUM IN HEART AND VASCULAR DISEASES J TEPLOFF and A KOSCHEWNIKOWA, Klin Wchnschr 8 1222, 1929

In heart and vascular diseases without insufficiency of circulation there is no variation in the Ca content. The K content usually is normal, sometimes it is increased, but the ratio K/Ca remains constant. During cardiac decompensation in most patients there is a diminution of the Ca content as well as the Cl and the inorganic P. The K content remains within the limits of normal. On the appearance of cardiac insufficiency especially with cardiosclerosis the relation between K and Ca in the serum varies from the normal and usually in an increase.

AUTHORS' SUMMARY

THE RESERVE ALBUMIN OF THE LIVER K PASCHKIS, Klin Wchnschr 8 1293, 1929

Rats on a high albumin diet are particularly resistant to insulin. The albumin granules of the liver disappear with large doses of insulin. Epinephrine also decreases the reserve albumin. Epinephrine and insulin combined have no effect on the reserve albumin. Possibly these substances affect metabolism differently. The reserve albumin is not influenced by thyroidin. Thymic preparations seem to favor storage of albumin.

AUTHOR'S SUMMARY

Microbiology and Parasitology

MENINGOCOCCUS ENDOCARDITIS H E MACMAHON and E A BURKHARDT, JR., Am J Path 5 197, 1929

A case of meningococcus endocarditis is reported with the autopsy and bacteriologic observations. A brief discussion deals with the clinical, pathologic and bacteriologic considerations of meningococcus endocarditis. The literature is reviewed.

AUTHORS' SUMMARY

A CASE OF MENINGITIS DUE TO ENDOMYCES CAPSULATUS (NEW SPECIES) ALLAN G REWBRIDGE, CARROLL W DODGE and THEODORE T AYERS, Am J Path 5 349, 1929

The clinical record and autopsy observations in a case of meningitis due to *Endomyces capsulatus* are reported. The organism was not found in the spinal

fluid The morphologic and cultural characteristics of *Endomyces capsulatus* are described The organism is pathogenic for mice but not for rabbits or guinea-pigs

AUTHORS' SUMMARY

THE PRESERVATION OF YELLOW FEVER VIRUS W A SAWYER, W D M LLOYD and S F KITCHEN, J Exper Med 50 1, 1929

The virus of yellow fever may be preserved for at least 154 days in the blood or liver tissue of infected monkeys if the material is dried in a vacuum while in the frozen state and kept in the refrigerator in sealed glass containers A gradual diminution of virulence is noticeable in the older specimens If infectious blood is dried in a vacuum at room temperature, instead of in the frozen state, and is stored in sealed containers in the refrigerator, the virus may survive as long as 155 days The virus may be preserved for at least thirty days in liver kept continuously frozen Storage of blood or liver in 50 per cent glycerin in the refrigerator will usually keep the virus alive for sixty days and may do so for 100 days, but with the injection of the older material there is a marked tendency toward lengthening of the incubation period and increase in the number of recoveries Yellow fever virus in citrated or clotted blood, when kept in the refrigerator, dies out rapidly In our experience the most satisfactory method of preserving strains of yellow fever virus in the laboratory, consists of freezing and drying blood taken from a monkey on the first day of an attack of experimental yellow fever and storing the dry material in sealed glass tubes in a cold place

AUTHORS' SUMMARY

FURTHER NOTES ON THE FILTRATION OF THE VIRUS OF VACCINIA HUGH K WARD, J Exper Med 50 31, 1929

An active filtrate can be obtained from vaccinia lesions by grinding up the fresh tissue with glass fragments, emulsifying in hormone broth, centrifuging the emulsion and filtering the supernatant fluid through a Berkefeld V filter The sterile filtrate so obtained has been shown by comparative titration on rabbits to have about one sixteenth of the activity of the nonsterile emulsion used in vaccination of human beings Centrifugation of such a filtrate shows a partial concentration of the virus in the lowermost layer The virus survives for a long time, if the filtrate is kept near the freezing point, and probably will survive indefinitely if kept frozen The addition of glycerin is not necessary

AUTHOR'S SUMMARY

ATTEMPTS TO REPRODUCE RHEUMATIC FEVER IN ANIMALS LOUIS GROSS, LEO LOEWE and BENJAMIN ELIASOPH, J Exper Med 50 41, 1929

Experiments have been described in which we attempted to reproduce in animals the lesions characteristic of rheumatic fever in man A large number of animals representing seven species was employed Among other materials streptococci isolated in pure culture from the blood of rheumatic patients (proved to be so by biopsy or by autopsy) as well as whole blood, plasma, serum, pericardial, pleural and hydrocele fluid, filtrates from tonsils, subcutaneous nodules, lymph nodes and nasopharyngeal washings obtained from such patients were used in a variety of combinations and with a number of procedures calculated to predispose the animal to the disease A discussion is given of the criteria the fulfilment of which is essential for the establishment of the experimental production of rheumatic disease in animals Judged by these criteria, we have failed to reproduce the disease This conclusion, we believe, holds true for all the work thus far reported in the literature

AUTHORS' SUMMARY

ON THE RELATION OF BACTERIA TO SO-CALLED "CHEMICAL PNEUMONIA" A R KOONTZ and M S ALLEN J Exper Med 50 67, 1929

The question of a causal relation of the bacteria in gassed lungs to the pneumonia present cannot be regarded as decided It may be said that the appearance

of gassed lungs in patients with pneumonia is similar to that in pneumonia of known bacterial origin. In a few cases the type of pneumonia found coincides with the reported cases of so-called "chemical pneumonia" which is characterized by a preponderance of epithelial cells in the exudate. Gassed lungs are not sterile but show highly varying numbers of bacteria. The bacteria are not intracellular and are not present in large numbers in the majority of cases. The arguments for and against a causal relationship between the bacteria and the pneumonia may be summarized. Against a causal relationship are (1) the early appearance of pneumonia after gassing, (2) the occurrence of pneumonia with small numbers of bacteria present and (3) the fact that few bacteria are engulfed by leukocytes in gassed lungs whereas large numbers are present in the pneumonias in nongassed subjects and are conspicuously intracellular. In favor of a causal relationship are (1) the presence of bacteria in any numbers, (2) the picture of bronchopneumonia presented is similar to bronchopneumonia of known bacterial origin and (3) pneumonias characterized by large numbers of epithelial cells in the exudate (so-called "chemical pneumonia") occur in animals that were never gassed or subjected to other irritating substances in any way.

AUTHORS' SUMMARY

STUDIES ON SOUTH AMERICAN YELLOW FEVER NELSON C. DAVIS and
RAYMOND C. SHANNON, J. Exper. Med. 50 81, 1929

Yellow fever virus from *M. rhesus* has been inoculated into a South American monkey (*Cebus macrocephalus*) by injection of blood and by bites of infected mosquitoes. The *Cebus* does not develop the clinical or pathologic signs of yellow fever. Nevertheless, the virus persists in the *Cebus* for a time as shown by the typical symptoms and lesions which develop when the susceptible *M. rhesus* is inoculated from a *Cebus* by direct transfer of blood or by mosquito (*A. aegypti*) transmission.

AUTHORS' SUMMARY

THE RÔLE OF CARBOHYDRATES IN BIOLOGICAL OXIDATIONS AND REDUCTIONS
EXPERIMENTS WITH PNEUMOCOCCUS RENE DUBOS, J. Exper. Med. 50 143,
1929

The reducing power of plain broth cultures of pneumococcus is largely dependent on the presence in the medium at the time when the reduction test is performed of certain metabolites. The washed cells of pneumococcus are able to reduce the various indicators of oxidation-reduction potentials in the presence of dextrose. The relative velocity of reduction of these indicators is determined by the number of cells used in the test, the concentration of the dyes and their position in the oxidation-reduction scale. Oxidized thiol compounds (glutathione, cystine, oxidized thioglycolic acid) are likewise rapidly reduced by dextrose in the presence of washed cells of pneumococcus. This pneumococcus-dextrose system is able to form peroxide under aerobic conditions. These substances which form peroxide in the presence of pneumococcus cells are also the ones which Cole found to be active in changing hemoglobin into methemoglobin under the same conditions. The power of washed cells of pneumococcus to reduce methylene blue in the presence of dextrose is dependent on at least two constituents: one which can be readily removed from the cell by washing. Sugar-free meat infusion will function instead of it. The other is inactivated more slowly by the process of washing and is destroyed by heating for ten minutes at 55°C. The interreaction between the dextrose and the cell seems to result in a fundamental reaction in which one molecule of dextrose becomes able to reduce rapidly one molecule of methylene blue. The existence of side-reactions often obscures this ratio. The significance of these observations is considered in relation to the nature and mechanism of the "activation" of metabolites, the preparation of synthetic mediums, the phenomena of growth and the meaning of the expression "reducing power of a bacterial culture."

AUTHOR'S SUMMARY

PERSISTENCE OF LIVING CELLS IN MAITLAND'S MEDIUM FOR THE CULTIVATION OF VACCINE VIRUS T M RIVERS, E HAAGEN and R S MUCKENFUSS, *J Exper Med* **50** 181, 1929

Cells survive for at least five days and at times are capable of multiplying in a mixture of serum and Tyrode's solution used by Maitland for the cultivation in vitro of vaccine virus

AUTHORS' SUMMARY

A STUDY OF PNEUMONIA IN A RURAL AREA IN SOUTHERN ALABAMA W G SMILLIE and E L CALDWELL, *J Exper Med* **50** 233, 1929

Pneumococcus type IV of low virulence was the prevailing organism in fifty-eight cases of pneumonia studied in southern Alabama. Fixed types of pneumococci were not common. Pneumonia was more prevalent in children from 5 to 15 years of age than in adults. As a rule, the disease ran a mild course. In most of the cases of pneumonia the patients gave a definite history of an acute cold antedating the attack of pneumonia by a period of from five to eight days. Exposure alone did not seem to predispose to pneumonia, but those with an acute cold who were exposed to chilling of the body surface frequently developed pneumonia. There were seven "family epidemics" of pneumonia. In each instance there was a family epidemic of colds antedating the pneumonia. The pneumococcus was found in large numbers in the nasopharynx of those suffering from colds as well as in the pneumonia patients. The epidemiology of pneumonia in the pioneer days of American history has many points in common with the epidemiology of pneumonia in a rural isolated area in southern Alabama today. This suggests that the crowded conditions and frequent contacts of modern city life have built up a community resistance to avirulent strains of pneumococci.

AUTHORS' SUMMARY

DISSOCIATION OF HOG BACILLUS C P LI, *J Exper Med* **50** 245 and 255, 1929

Four forms of the hog cholera bacillus are described, namely the "normal" type strain, and three variants.

THE EFFECT OF CATAPHORESIS ON POLIOMYELITIS VIRUS P K OLITSKY, C P RHOADS and P H LONG, *J Exper Med* **50** 273, 1929

Under ordinary conditions of hydrogen ion concentration the virus of poliomyelitis, as such, or associated with particles in fine suspensions, migrates in an electrical field to the anode. It follows that the virus bears an electronegative charge. By means of cataphoresis, the virus can be recovered from a noninfective mixture of virus and specific immune serum. By the same means it is possible to reveal the presence of virus in the central nervous system of a monkey which has recovered from the active stage of experimental poliomyelitis.

AUTHORS' SUMMARY

ADAPTATION OF MASTITIS STREPTOCOCCI TO MILK F S JONES and H S SIMMS, *J Exper Med* **50** 279, 1929

The data here presented indicate that the inhibitory principle affecting the growth of streptococci in milk is not greatly utilized during the lag phase, and that the abrupt termination of lag is not due to the utilization of the principle. They further indicate that the sudden beginning of growth cannot be ascribed to a resistant type of streptococcus present in the culture from the first, but to an adaptation occurring during the lag phase. The addition of large numbers of dead or living streptococci to milk, for limited periods, fails to diminish appreciably the inhibitory principle.

AUTHORS' SUMMARY

THE EFFECT OF EXTRACTS OF ORGANS ON THE INFECTING POWER OF VACCINE VIRUS F DURAN-REYNALS, J Exper Med **50** 327, 1929

Brain and testicle tissue from immune rabbits brought in contact with the Levaditi or Noguchi strains of vaccine virus will fix or inactivate the virus. Extracts of normal testicles from susceptible animals enhance to an extraordinary degree the infectivity of both the neuro and the dermal strains of vaccine virus. The Noguchi virus is not affected by testicle extracts when injected into the skin, but kidney extract has a definite enhancing power on the strain when injected into either skin or testicle. The effect of tissue extracts seems to be on the cells of the host rather than on the virus. This is indicated by the fact that virus injected intravenously localizes most readily in an area of skin previously injected with testicle extract. Furthermore an enhanced lesion results if the virus is injected into an area as long as three days after the area has been injected with testicle extract. The augmenting substance of the tissue extracts is little affected by high dilutions, passes through a Berkefeld V candle and is carried down with the proteins precipitated by weak acids. Rabbits with enhanced lesions show general symptoms and about 25 per cent die with generalized vaccinia. Kidney, and probably skin, brain and liver extracts possess enhancing properties, but to a much less degree than the testicle. On the other hand, spleen, blood and probably lymph nodes and bone marrow not only fail to produce enhancement, but actually restrain or even suppress entirely the vaccinal skin infection.

AUTHOR'S SUMMARY

A STUDY OF THE GENERALIZATION OF VACCINE VIRUS FROM ENHANCED SKIN LESIONS FRLED W STEWART and F DURAN-REYNALS, J Exper Med **50** 341, 1929

Rabbits bearing intensive skin lesions resulting from the intracutaneous injection of neurovirus plus testicular extract show typical histologic alterations in the gonads, suprarenal glands, liver, spleen, lung, lymph nodes and bone marrow. Similar but less widespread alterations are found after intravenous injection of neurovirus. Although testicle extract injected intracutaneously with neurovirus has a marked enhancing action on the activity of the latter, the same mixture injected intravenously yields no sign of any such enhancement. The significance of these observations as regards the question of the ectodermotropism of vaccine virus is discussed, and the doctrine of specific organ affinities is considered.

AUTHORS' SUMMARY

PARALYSIS IN GUINEA-PIGS BY THE TUBERCLE BACILLUS PAUL A LEWIS and RICHARD E SHOPE, J Exper Med **50** 365, 1929

When a strain of human tuberculosis was carried from guinea-pig to guinea-pig by intracerebral inoculation, the bacillus of tuberculosis could be readily recovered in the semisolid *Leptospira* medium of Noguchi simply modified by the substitution of guinea-pig for rabbit serum. Whether even this modification is required remains to be determined. The tubercle bacillus in these cultures and possibly in the nerve tissue as well differed from the classic type in that it was less acid-fast and lacking in alcohol fastness. However, it retained the Gram stain as modified by Much. Staining reactions, as this culture of the tubercle bacillus shows, are not absolute qualities but are variable with conditions, a consideration which it may be important to recognize. Efforts to define these conditions more precisely are likely to be productive.

AUTHORS' SUMMARY

LECITHIN AND STREPTOCOCCAL HEMOLYSIS J GORDON and F R STANSFIELD Brit J Exper Path **10** 191, 1929

Lecithin added to cultures of hemolytic streptococci neutralizes the hemolytic activity. Treatment with ligrome does not remove or destroy hemolysin. The hemolytic activity of streptococcal cultures cannot be restored by treatment with a lecithin solvent (ligrome) after it has once been destroyed by addition of lecithin.

AUTHORS' SUMMARY

NOTES ON INFECTIOUS MYXOMATOSIS OF RABBITS G M FINDLAY, Brit J
Exper Path **10** 214, 1929

The symptoms and pathologic changes in infectious myxomatosis of rabbits are described. In the connective tissue cells of the lesions certain minute granules are present which may possibly represent the actual virus.

AUTHOR'S SUMMARY

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A *PENICILLIUM*, WITH
SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B INFLUENZAE*
ALEXANDER FLEMING, Brit J Exper Path **10** 226, 1929

A certain type of *Penicillium* produces in culture a powerful antibacterial substance. The antibacterial power of the culture reaches its maximum in about seven days at 20 C and after ten days diminishes until it has almost disappeared in four weeks. The best medium found for the production of the antibacterial substance has been ordinary nutrient broth. The active agent is readily filtrable and the name "penicillin" has been given to filtrates of broth cultures of the mold. Penicillin loses most of its power after from ten to fourteen days at room temperature but can be preserved longer by neutralization. The active agent is not destroyed by boiling for a few minutes, but in alkaline solution boiling for one hour markedly reduces the power. Autoclaving for twenty minutes at 115 C practically destroys it. It is soluble in alcohol but not in ether or chloroform.

The action is marked on the pyogenic cocci and the diphtheria group of bacilli. Many bacteria are insensitive, e.g. the coli-typhoid group, the influenza-bacillus group and the enterococcus. Penicillin is nontoxic to animals in enormous doses and is nonirritant. It does not interfere with leukocytic function to a greater degree than does ordinary broth. It is suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with microbes sensitive to penicillin. The use of penicillin on culture plates renders obvious many bacterial inhibitions which are not evident in ordinary cultures. Its value as an aid to the isolation of *B influenzae* has been demonstrated.

AUTHOR'S SUMMARY

CRITICISM OF RANKE'S TEACHING OF THE STAGES IN TUBERCULOSIS, PARTICULARLY OF RANKE'S SECONDARY STAGE W BLUMENBERG, Beitr z klin
d tuberk **71** 385, 1929

This paper is primarily a rather violently polemic criticism of Ranke's concepts. The refutation of Ranke's work is, in part, of a highly theoretical nature and unsuitable for reproduction in a short abstract. The author's points of view are supported by observations at autopsy in a rather large number of cases, some of which are reported in detail. The conclusions are that Ranke's teachings are wrong in toto, and that it is impossible to differentiate various stages in the development of tuberculosis.

MAX PINNER

PHTHISIS OF THE SUBPLEURAL LYMPH NODES F SCHMOE, Beitr z klin d
Tuberk **71** 449, 1929

Subpleural lymph nodes constitute, normally, an important connecting link between the superficial and the deep lymphatic system of the lung. On account of their location, they play an important role, both in aerogenous and hematogenous propagation of tubercle bacilli. Subpleural lymph nodes, in the vicinity of primary foci, may become infected and present, then, the picture which is known in the primary complex of lymph glands. These glands, however, become much more frequently involved if a hematogenous spread occurs subsequent to the primary infection, that is in endogenous reinfection. In such cases, these lymph glands present the histologic picture which is characteristic for reinfection foci. The subpleural lymph glands protect the greater circulation from hematogenous infection. It is pointed out that tuberculous scars in these lymph nodes are sometimes the only demonstrable reinfection foci.

MAX PINNER

PERIFOCAL HEMORRHAGES IN TUBERCULOSIS L SIMONSON, Beitr z klin d Tuberk **71** 467, 1929

In four cases of tuberculosis, in different organs, hemorrhages in the immediate vicinity of tuberculous foci are reported. They are probably the result of several factors, such as stasis, specific toxins and allergy

MAX PINNER

A CASE OF SEPSIS TUBERCULOSA GRAVISSIMA (AVIAN TUBERCULOSIS?) M DUGGI, Beitr z klin d Tuberk **71** 538, 1929

A woman, aged 65, died three days after admission and eleven days after the onset of clinical symptoms. The symptomatology was of such a nature that typhoid fever was diagnosed, although serologic and bacteriologic tests were negative. At autopsy, many tumor-like nodules were found scattered throughout the spleen and liver. The mesenteric and bronchial lymph nodes were much enlarged. There were many emboli in the smaller branches of the pulmonary artery. Histologically, it was found that all the nodules consisted of focal necroses which contained large numbers of acid-fast rods. Microscopic foci of similar nature were found in the stomach and in the ileum. The organism was apparently avirulent for guinea-pigs and mice. They grew much faster than human tubercle bacilli. Although the organism was not definitely identified, it is concluded that it must have been a tubercle bacillus of the avian type.

MAX PINNER

THE PROBLEM OF BARTONELLA INFECTION OF RATS E LAUDA and F MARCUS, Centralbl f Bakteriologie **107** 104, 1928

The authors discuss the problem as to the nature of the virus concerned in the infectious anemia of rats, and conclude from their experiments in which various drugs causing hemolysis were used that the so-called *Bartonella* bodies are not degeneration products but are probably organisms as claimed by M. Mayer.

PAUL R. CANNON

THE MECHANISM OF TRICHINA INFECTION JULIAN H. LEWIS, Centralbl f Bakteriologie **107** 114, 1928

Lewis shows that the poorer muscles are in glycogen the greater the invasion by *Trichinae*. Guinea-pigs injected frequently with insulin and then infected showed a much heavier infestation with *Trichinae* than did the normal controls. Conversely, dextrose feeding of such animals favored a lighter infestation. The author believes that the organotherapy of *Trichinae* is best explained by some chemotactic substance resulting from the catabolism of glycogen.

PAUL R. CANNON

THE REACTION OF VARIOIA VACCINE-VIRUS IN TISSUE CULTURE. E. HAAGEN, Centralbl f Bakteriologie **109** 31, 1928

Vaccine virus in rabbit-testis tissue culture developed well provided it was freshly explanted every four or five days. The virulence of the virus cultivated in this manner for eight months through thirty-seven passages remained for the most part unchanged, and in a few cases, even, increased.

PAUL R. CANNON

THE INFLUENCE OF JENSEN SARCOMA ON THE INFECTIOUS ANEMIA OF RATS W. KIKUTH, Centralbl f Bakteriologie **109** 51, 1928

Kikuth attempted to confirm the observations of Hirschfeld and Tinazzi that, in rats in which Jensen sarcomas were implanted, splenectomy led to less serious effects from the development of *Bartonella* anemia. The latter observers suggested that the tumors either secreted protective substances against the agent of the

anemia, or stimulated the reticulo-endothelial system in some manner. Nine rats were injected with Jensen sarcoma and later splenectomized. Nine normal rats served as controls. All of the rats with tumor developed *Bartonella* anemia, although the death rate was not so rapid as in the controls. Kikuth concluded that the somewhat less marked susceptibility of the rats injected with sarcoma to the development of the anemia following splenectomy is best explained by the fact that in these animals there is more stimulation of the bone marrow and more blood regeneration than in normal animals. As a result, the development of the bartonella virus is somewhat restrained.

PAUL R. CANNON

THE RÔLE OF BED-BUGS (*CIMEX LECTULARIUS*) AND TICKS (*ORNITHODORUS MOUBATA*) IN THE TRANSMISSION OF ANTHRAX. H. P. ROSENHOLZ and O. W. OWSJANNIKOWA, *Centralblatt Bakteriologie* **110** 160, 1929.

The bite of bed bugs and ticks which had been infected with anthrax bacilli caused no infection in white mice. In some insects, however, anthrax infection persisted in the gastro-intestinal tract for as long as one month. The feeding of such insects with blood from anthrax-sick animals led to the passage of anthrax bacilli into the body cavity where the organisms multiplied. In the dead bodies of such insects the anthrax bacilli remained alive for as long as six months.

PAUL R. CANNON

HYDROGEN ION CONCENTRATION IN THE BLOOD OF TUBERCULOUS RABBITS. H. ZAIN, *Ztschrift für Tuberkulose* **53** 215, 1929.

The pH values in the blood of tuberculous rabbits are within the limits of normal variation. This is true for both slightly and severely diseased animals. Only occasionally are values found which are slightly below the normal.

MAX PINNER

END-RESULTS IN METAL SALT THERAPY IN TUBERCULOSIS IN RABBITS. L. E. WALBUM, *Ztschrift für Tuberkulose* **53** 292, 1929.

In all these experiments which cover a period from 1925 to 1929, rabbits were infected with 0.0001 mg. of bovine bacilli intravenously. The treatment with the various salts was started thirty-three days after the infection, that is at a period at which the tuberculous disease was fairly well advanced. Forty-two different metals were examined, but only two were found namely, cadmium and manganese, which had a definite and specific therapeutic action. Eight other ones (cerium, barium, aluminum, lanthan, molybdenum, platinum, nickel and samarium) had a weak therapeutic action. All the other ones remained without influence on the development of tuberculosis.

MAX PINNER

THE FATE OF BCG IN THE ORGANISM. W. A. LUBARSKI, *Ztschrift für Tuberkulose* **53** 427, 1929.

After the injection of 5 mg. of BCG into guinea-pigs, acid-fast organisms could be demonstrated for from six to eight months. Bacteriolysis was not observed. The organisms disappear after decomposing into granules and by excretion through the intestinal canal. This indicates that revaccination in children should be done after one year.

MAX PINNER

THE RESISTANCE OF TUBERCLE BACILLI AGAINST EXTERNAL INJURIES. R. BIELING, *Ztschrift für Tuberkulose* **53** 512, 1929.

A rather dense but homogenous suspension of tubercle bacilli was kept in water of 70 degrees for one-half hour, and was kept twice in boiling water for one-half hour, then 0.5 per cent phenol was added. Five guinea-pigs received 1 cc. sub-

cutaneously on three successive days. One of these five guinea-pigs developed tuberculin allergy and was killed ten weeks after the injection. Its lymph glands were much enlarged but not caseated. Tubercle bacilli could not be demonstrated in the glands. Two other guinea-pigs were injected with the lymph glands and the spleen of the first animal. The animal injected with the material from the lymph glands developed generalized tuberculosis. In a second experiment, it was found that some tubercle bacilli remained alive, although with much lowered virulence, after the following treatment. Broth cultures were kept fifteen minutes in the autoclave at 102 degrees. After this, they were heated to from 70 to 80 degrees for at least six hours. The bacillary mass was filtered off and kept in 70 per cent alcohol for several months. These experiments would indicate a much higher degree of resistance in tubercle bacilli than that usually reported, and they show the importance of testing more than one animal, in order to prove the effectiveness of sterilization procedures.

MAN PINNLR

FUNGI AS THE CAUSE OF ABORTION IN CATTLE. H. C. BENDIXEN and N. PLUM,
Acta path et microbiol Scandinav 6 252, 1929

Seventeen cases of abortion in cows were studied and cultures made from the placentae. *Aspergillus fumigatus* was isolated in eight cases, *Absidia iamosa* in two cases and both organisms in the remaining seven. When both organisms were isolated, it is highly probable that only one was the causative agent and that the other was present as the result of contamination after birth. Microscopically, the hyphae were found in the placental tissue where they had caused widespread necrosis and considerable exudation. Macroscopically the cotyledons were composed of a yellowish-gray or brownish necrotic tissue, which is characteristic of the disease. Five pregnant cows were injected intravenously with the spores or conidia of the organisms, and in all cases the same pathologic changes occurred in the placentae as were found following the natural disease.

Immunology

EXPERIMENTAL PERITONITIS AND PERITONEAL IMMUNITY. S. F. HERRMANN,
Arch Surg 18 2202, 1929

The author conducted several experiments in an attempt to produce a peritoneal immunity to infection, chiefly of *B. coli* and of streptococci. Intraperitoneal injection of colon bacilli was carried out, and some degree of resistance to infection from feces was obtained. Intraperitoneal injection of a vaccine of streptococci and colon bacilli was also carried out, mainly on rabbits, and 80 per cent of the rabbits so immunized survived infection from fecal soiling of the peritoneal cavity. It was seen that the protection was due to local immunization, because rabbits injected with the same vaccine subcutaneously were not so protected. The author was able to show a high degree of positive blood cultures in rabbits dying of peritonitis. There was a much higher number of positive blood cultures in those in which peritonitis did not develop after soiling of the peritoneal cavity by fecal contents, indicating that the reaction of the peritoneum, or in other words, the development of peritonitis, constitutes a local defense mechanism.

N. ENZER

THE EFFECT OF REPEATED INJECTIONS OF EPINEPHRINE ON THE HEMOLYSIN FORMATION IN SUPRARENALECTOMIZED RATS. DAVID PERLA and J. MARMORSTON-GOTTESMAN, *J. Exper. Med* 50 87, 1929

Epinephrine diluted with physiologic salt solution or with isotonic dextrose solutions and injected in amounts of 0.2 mg per kilogram of body weight twice daily into suprarenalectomized rats raises their antibody-forming capacity. This result is not entirely dependent on the effect of the diluting fluid.

AUTHORS' SUMMARY

IMMUNOLOGICAL STUDIES IN RELATION TO THE SUPRARENAL GLAND J
MARMORSTON-GOTTESMAN and DAVID PERLA, J Exper Med **50** 93, 1929

Suprarenalectomy is followed by a disturbance in the antibody-forming mechanism of the body. The suprarenal gland plays a rôle in the water metabolism of the tissues. Restoration of the water exchange in the tissues to a normal level is sufficient to raise the antibody-forming capacity to normal.

AUTHORS' SUMMARY

THE PRODUCTION AND TITRATION OF POTENT HORSE ANTIPNEUMOTOXIN
JULIA T PARKER and MARY VAN S MCCOY, J Exper Med **50** 103, 1929

The serum of horses immunized with increasing doses of certain anaerobically produced autolysates of pneumococci contain potent neutralizing antibodies for the pneumotoxin. The method for the in vitro titration of these horse antipneumotoxic serums is given.

AUTHORS' SUMMARY

EFFECT OF ANTI-AUTOLYSATE SERA ON PNEUMOCOCCUS PNEUMONIA IN GUINEA
PIGS JULIA T PARKER, J Exper Med **50** 161, 1929

Antipneumotoxic serums prepared in rabbits or horses by immunization with sterile filtrates of the pneumotoxin, under certain conditions protect against the pneumonia caused by the intratracheal injections of mixtures of living pneumococci and toxic autolysates. The protection against the development of pneumonia is heterologous, at least as regards type I. Type 2, an anti-autolysate serum prepared by the immunization with a pneumotoxin from one type of pneumococcus will prevent the development of pneumonia caused by the injection of pneumococci and autolysate from another type. Certain antipneumococcus horse serums used in the treatment of pneumonia in man, contain either no heterologous pneumonia-preventing antibodies or slight amounts only. These serums, however, protect against the pneumonia produced by injections of pneumococci and pneumotoxin of the homologous strain, the degree of protection depending on the amount of specific protective substances such serums contain. Antipneumotoxic serums produced in rabbits or horses by the injection of sterile Berkefeld filtrates of the toxic autolysates contain no pneumococcus specific protective substances.

AUTHOR'S SUMMARY

RELATION OF VACCINAL IMMUNITY TO THE PERSISTENCE OF THE VIRUS IN
RABBITS PETER K OLITSKY and PERRIN H LONG, J Exper Med **50** 263,
1929

By means of cataphoresis vaccine virus can be obtained from suspensions of tissue which are inactive by the usual tests of animal inoculation. Active virus can be obtained by cataphoresis from the tissues of rabbits long recovered from the effects of cutaneous vaccination. Evidence is brought forward which suggests that immunity in a virus disease, such as vaccinia, may be linked with the persistence in the body of living virus.

AUTHORS' SUMMARY

THE REMOVAL OF AGGLUTININ FROM SENSITIZED MOTILE BACTERIA JOHN B
NELSON, J Exper Med **50** 377, 1929

The salt-free water washings of a sensitized motile bacterium (*B. acitrycke*) were found to cause a floccular agglutination in the presence of both whole and deflagellated antigen. Evidence was presented that the water washings when salt-free contained flagella and flagellar agglutinin and that clumping occurred on the addition of saline. The floccular reaction in the presence of deflagellated bacteria was regarded as the agglutination of flagella present in the washings. In the presence of whole bacteria, however, actual bacterial agglutination resulted.

AUTHOR'S SUMMARY

ON ISOAGGLUTININ REACTIONS OF HUMAN BLOOD OTHER THAN THOSE
DEFINING THE BLOOD GROUPS K LANDSTEINER and PHILIP LEVINE,
J Immunol **17** 1, 1929

A study was undertaken on the occurrence of atypical iso-agglutinin reactions of human blood. Such a technique was purposely chosen as would detect serums of even slight activity. In this way rather numerous irregular reactions were found in a material obtained from patients with mental diseases. Most of the reactions observed may be put under the heading of cold agglutination, that is, the serums are active only at low temperature and give weak agglutination at room temperature (20 degrees). A smaller number of serums (about 3 per cent) contained agglutinins of a type intermediate between cold agglutinins and typical iso-agglutinins since their reactions were distinctly noticeable also under the usual conditions of blood grouping. In all of the cases with atypically reacting serums the blood cells showed no abnormal behavior and could readily be grouped. Also the grouping of the serums was not interfered with by the presence of the irregular agglutinins. Hence the irregularities are superimposed on the much more prominent group properties, and are not in conflict with the scheme of the four blood groups, the usefulness of which cannot be questioned (Thomsen). With regard to the practice of transfusions, it may be stated that in several instances in which the serum of the recipient contained irregular agglutinins for the blood of the donor no untoward symptoms were observed. Several serums of groups O, A and B, described, had agglutinins which were similar with regard to their specificity. In groups A and AB two types of agglutinins were found specific in general for cells of one or the other subgroup of group A, those agglutinating blood AA² showed in addition a specific action on cells of group O (Schnff). The properties of these serums demonstrate again definitely the existence of subgroups in group A, a distinction hardly significant at present for practical purposes. The results with the abnormal agglutinins of human serums give further support to the conclusion that there exists a great number of individual differences of human blood.

AUTHORS' SUMMARY

THE SPECIFICITY OF MAMMALIAN SPERMATOZOA, WITH ESPECIAL REFERENCE
TO ELECTROPHORESIS AS A MEANS OF SEROLOGICAL DIFFERENTIATION
STUART MUDD and EMILY B. H. MUDD, J Immunol **17** 39, 1929

Spermatozoa of man, rat, guinea-pig, bull and ram injected into rabbits induce the production of antibodies which are species specific. Cross reactions occur between bull and ram spermatozoa and their corresponding antisera. Inconclusive evidence is found of cross reaction between antirabbit sperm serums and guinea-pig spermatozoa. Electrophoresis, in spite of technical difficulties in working with spermatozoa, is found to be an adequate means of making these serologic differentiations. In confirmation of other investigators, antirabbit sperm antibodies have been induced by intravenous injection of rabbit spermatozoa into rabbits. Mammalian spermatozoa therefore possess both species and tissue specificity.

AUTHORS' SUMMARY

THE REACTION OF THE WHITE BLOOD CELLS TO SPECIFIC PRECIPITATES
H. W. CROMWELL and J. A. CENTENO, J Immunol **17** 53, 1929

When fresh normal citrated blood is mixed with a protein and its specific antibody, the polymorphonuclears, lymphocytes and mononuclears become strikingly vacuolated. This vacuolation is definitely associated with the product of the antigen-antibody reaction since it does not occur if the precipitate is removed before the whole blood is added, and the reaction does occur when the whole blood is added to the thoroughly washed precipitate suspension. Nonspecific particulate matter, as heat-coagulated protein, collodion particles and charcoal particles, does not stimulate the reaction. Phagocytosis of sensitized *B. typhosus*

and pneumococcus by the same types of cells has been observed with marked vacuolation of the polymorphonuclears and mononuclears. The vacuolation appears more slowly than with the specific precipitate and seems not to occur in the lymphocytes. It is considered that the specific precipitate is probably phagocytosed and that the vacuoles are associated in some manner with its subsequent digestion. These observations are significant in pointing out the probable importance of phagocytosis in determining the fate of the specific precipitate in vivo.

AUTHORS' SUMMARY

THE SIGNIFICANCE OF BRUCELLA ABORTUS AGGLUTININS IN HUMAN SERUM
C. M. CARPENTER, RUTH BOAK and O. D. CHAPMAN, J. Immunol. **17** 65, 1929

Agglutination tests for evidence of *B. abortus* infection on the serum collected from 4,050 Wassermann samples in Syracuse, N. Y., showed 73 per cent to contain abortus agglutinins. An examination of 955 similar samples of serum collected in New York City showed 24 per cent to agglutinate a *B. abortus* antigen. *B. abortus* agglutinins could not be demonstrated in the serum from adults who had been drinking pasteurized milk containing such antibodies. Evidence is submitted to indicate that *B. abortus* agglutinins in the blood serum are a result of an active production by the living organism which has invaded the tissues of the body. *B. abortus* agglutinins may disappear from human serums slowly. One serum titer was 1:405 two years after apparent recovery from undulant fever. Because of the variable antigenic properties of certain strains of *B. abortus* no specific serum titer can be established as diagnostic of undulant fever.

AUTHORS' SUMMARY

RELATIONSHIP OF SCHULTZ-CHARLTON REACTION AND SERUM DILUTION
MARGARET E. WYLIE, J. Infect. Dis. **45** 1, 1929

The blanching power of a given serum is not directly proportionate to its dilution or concentration. With dilute solutions the results are unreliable, although positive results may occasionally be obtained. In practice it is inadvisable to use a dilution higher than 1:100. If the serum is diluted, it matters little whether the strength used is 1:10 or 1:100. The most accurate results are given by undiluted serum.

The time interval between the initial injection and the appearance of blanching varies within wide limits from one to forty-eight hours.

The Schultz-Charlton technic cannot be regarded as even a rough method of estimating the potency of a serum.

AUTHOR'S SUMMARY

EFFECT OF HEATING SYPHILITIC SERUM AND ITS PROTEIN FRACTIONS ON PRECIPITATION REACTION
M. NISHIO, J. Infect. Dis. **45** 148, 1929

Globulin from syphilitic serum, whether unheated or heated for thirty minutes at 56°C, gives precipitation results with the Kahn test, similar to those given by the same syphilitic serum after heating for thirty minutes at 56°C.

Unheated albumin from syphilitic serum prevents or reduces precipitation given by the globulin. This property is not manifested when the albumin is heated for thirty minutes at 56°C.

The protection to precipitation exerted by unheated albumin appears to be an inverse function of the concentration of the reacting substances of the serum and antigen.

AUTHOR'S SUMMARY

STUDIES IN ANTIRABIES IMMUNIZATION
G. STUART and K. S. KRICKORIAN, J. Hyg. **29** 1, 1929

Statistical evidence and animal experiment have alike proved carbolized killed antirabies vaccine to be of undoubted efficacy in both pre-infectional and

postinfectious treatment Statistical evidence is furnished by the results of treatment of 90,000 patients, while experimental proof rests partly on the resistance shown by immunized animals to artificial infections with street virus, and partly on an estimation of degree and duration of rabicidal properties in their serums

The Bordet-Gengou reaction is of no value as a qualitative or quantitative test for the estimation of antirabies immunity

The efficacy of killed carbolized vaccine and probably of other antirabies vaccines is largely dependent on the concentration of the dosage and the period within which it is administered Better results follow the giving of small doses over a number of days than the giving of larger doses over a shorter period

It is impossible to reduce below a certain limit the time over which the total quantity of vaccine ordinarily sufficient for complete immunization can be usefully administered

The effect on rabbits of the subcutaneous injection of freshly fixed virus is dependent on the quantity of virus introduced and on the duration of its period of administration Few inoculations are more likely to cause death than several repeated inoculations ordinarily confer immunity Immunity thus acquired must have been produced within eleven or twelve days

AUTHORS' SUMMARY

FATAL REACTION FROM TRANSFUSION OF BLOOD L J WITTS, *Lancet* **1** 1297, 1929

An instance is reported of death from "hemoglobin infarction of the kidneys" following transfusion The preliminary test-grouping and cross-agglutination did not indicate any incompatibility on the part of donor and recipient

INVESTIGATION CONCERNING THE BLOOD GROUPS OF HORSES S SCHERMER, *Ztschr f Immunitätsforsch u exper Therap* **58** 130, 1928

Iso-agglutinins were found which showed two different blood corpuscle and two corresponding serum properties They occurred in four combinations In 16 per cent of fifty horses examined the blood could not be placed in any of these groups Their blood gave reactions which, with only two known factors, could not be worked out

The agglutinins of horse blood are weak, and the author states that consequently it is not always possible to estimate the blood group of a horse He also states that with the knowledge of blood groups race differences are determinable

ROY C AVERY

THE TECHNIC OF THE RIECKENBERG-BRUSSIN REACTION W P JAKIMOW, *Ztschr f Immunitätsforsch u exper Therap* **58** 413, 1928

The adhesive power of the immune bodies is strengthened by addition of a drop of normal citrated blood The serum of rats and rabbits immunized with killed cultures of *S recurrentis*, exhibited the adhesion phenomenon, in like manner as the serum from animals that have recovered from infection Plasma and serum from an animal infected with a strain contains immune bodies not only against that strain but also against the original strain Antibodies (thrombocytobarin) producing the adhesion phenomenon can be transferred passively to healthy animals

ROY C AVERY

THE FUNCTION OF THE RETICULO-ENDOTHELIAL SYSTEM IN CHEMOTHERAPEUTIC ACTION AND ITS INDEPENDENCE OF THE PROTECTIVE FUNCTION I L KRITSCHESKI, *Ztschr f Immunitätsforsch u exper Therap* **59** 1 1928

An unrecognized function of the reticulo-endothelial system is described in earlier papers by the author and by Meersohn This function determines the

curative action of chemical preparations and rests on the capacity of these cells to absorb the therapeutic agent and to release it gradually to the blood stream. In splenectomized animals, the chemotherapeutic effect is stronger if the arsenical preparation is used with 6 per cent agar instead of physiologic salt solution because the subcutaneously injected agar is supposedly similar in its action to the spleen, in that it absorbs the chemical preparation and only gradually releases it to the blood.

ROY C AVERY

IMMUNIZATION OF APES WITH BCG F GERLACH and R KRAUS, *Ztschr f Immunitätsforsch u exper Therap* **59** 306, 1929

The subcutaneous injection of from thirty to fifty mg of Bille Calmette Guérin strain was tolerated well by apes without injury. The animals possessed an immunity against subsequent tuberculous infections of both the bovine and the human types. Seven control apes showed typical progressive tubercular lesions at the point of inoculation, while ten immune apes, treated subcutaneously with BCG were able to withstand a virulent infection and showed no lesions.

The authors believe not only that progressive tubercular lesions produced by virulent and pathogenic strains give rise to immunity against infection, as previously thought, but also that attenuated, tuberculogenic but not pathogenic bacilli which produce a local benign lesion can give rise to immunity against virulent strains of the human and bovine type.

ROY C AVERY

THE COMPLIMENT CONTENT IN SERUM OF GUINEA-PIGS FED ACID AND ALKALINE FOODSTUFFS W E HILGERS and H ZAIN, *Ztschr f Immunitätsforsch u exper Therap* **59** 517, 1928

The compliment content in serum from guinea-pigs which are fed alkaline or acid diet in such a manner that they do not lose weight, shows no difference capable of proof when contrasted with normally fed animals of equal weight. In one case, lipemia developed in an animal fattened with oats which showed a diminution of compliment in its serum.

ROY C AVERY

A CRITIQUE OF THE HIRSZFELD HYPOTHESIS CONCERNING THE GENETIC RELATIONSHIPS BETWEEN BLOOD GROUP AND SCHICK REACTION E ROSING, *Ztschr f Immunitätsforsch u exper Therap* **59** 521, 1928

The author has shown that there exists no genetic relationship between blood group and the Schick reactions of parents and children. Only twenty-three of fifty children showed a Schick reaction similar to that of the parent to whose blood group they belong, while the remaining twenty-seven were different. The results do not confirm Hirszfeld's observations.

ROY C AVERY

THE INTRA-OCULAR INFECTION OF RABBITS WITH BCG N FUJIOKA and A FUCHS, *Ztschr f Immunitätsforsch u exper Therap* **60** 121, 1929

The authors have again shown that the BCG strain by intra-ocular infection in rabbits is biologically different from the virulent bovine type in that it produces a benign localized process, which shows a tendency to heal completely.

ROY C AVERY

MOUSE INFECTION WITH BCG AND TRANSMISSION TO GUINEA-PIGS N FUJIOKA, *Ztschr f Immunitätsforsch u exper Therap* **60** 125, 1929

Tubercle bacilli of the human, bovine and avian types and also the BCG strain could be cultivated from the organs of mice several months after peritoneal infection.

Organ emulsions of mice injected several months previously with human and bovine types were found to be infectious for guinea-pigs. The BCG strain could not be transmitted in this manner.

ROY C AVERY

HISTAMINE SUSCEPTIBILITY AND ANAPHYLACTIC REACTIONS G W SCHMIDT and A D STAHELIN, *Ztsch f Immunitätsforsch u exper Therap* **60** 222, 1929

The minimal dose of histamine chloride was determined for guinea-pigs by different routes of injection. Intravenous injection proved the more effective mode of administration.

The symptomatology of acute histamine shock is always the same regardless of the route by which it is administered.

The histamine sensitiveness in animals generally parallels their susceptibility to anaphylactic reaction. The author believes the results for the most part contradict the theory that anaphylactic symptoms are produced through histamine or histamin-like substances.

ROY C AVERY

THE ACTIVATION OF FORSSMAN ANTIGENS C HALLAUER, *Ztsch f Immunitätsforsch u exper Therap* **60** 293, 1929

The author shows that the euglobulin or pseudoglobulin fraction of rabbit serum like the whole serum itself when mixed with horse kidney extract and injected into rabbits does not activate the Forssman antigen. Pig plasma functions as well as pig serum in the process of activation.

ROY C AVERY

SYPHILIS FROM BLOOD TRANSFUSION J FREUCHEN, *Ugesk f Læger* **91** 386, 1929

Three cases of syphilitic infection in the course of blood transfusion are cited. In one case the donor became infected. The cannula first used for the patient having been removed and then by mistake placed in the vein of the donor.

Tumors

ADENOMA OF THE COIL GLANDS M H GOODMAN, *Arch Dermat & Syph* **20** 10, 1929

This is a report of an adenoma of the axillary sweat glands. The tumor occupied the position in the cutis where sweat glands are usually present. Normal coil gland structures were associated with the adenomatous and cystadenomatous elements. There was evidence of persisting function in some of the hyperplastic glandlike structures. The belief that the tumor arose from apocrine gland tissue rests on the demonstration of iron pigment in the cells by the Turnbull reaction in sections. The exocrine glands do not secrete iron.

FRANK M COCHENS

PROPERTIES OF THE CAUSATIVE AGENT OF A CHICKEN TUMOR F DURAN-REYNALS and JAMES B MURPHY, *J Exper Med* **50** 315, 1929

Ground muscle from susceptible chickens fixes in vitro in a proportion of instances the agent of the filtrable chicken tumor I, and in a lesser degree inactivates it, whereas the muscle from resistant animals, such as the rabbit and pigeon, is without effect. It is shown that the power of fixation of the chicken muscle is far greater than its inactivating properties. Brain and liver from the chicken, rabbit and pigeon seem devoid of any action on the agent. The desiccated chicken muscle tissue shares the properties of the fresh organ and the process of desiccation does not release the agent from the inactive or slightly active mixture of fresh muscle and filtrate.

AUTHORS' SUMMARY

ENDOMETRIOSIS IN UTERINE CORNUA MARION DOUGLASS, *Surg Gynec Obst* **49** 138, 1929

Cornual adenomas of the uterus were found in five of twelve specimens. The patients had not undergone any previous pelvic operation. This contradicts the

postsalpingectomy theory of Sampson in which it is supposed that there is direct operative implantation of endometrial or tubal mucosa or regurgitation of menstrual blood through the fimbria of the tubes. The author agrees with Novak that the primitive celomic mesothelium is concerned in the histogenesis of endometriomas and regards the regurgitation of menstrual blood as infrequent. The association of inflammation in these specimens may bear some relation to these glandlike structures of the uterus.

RICHARD A. LIFVENDAHL

THYROID TUMORS OF THE OVARY G. L. MOENCH, Surg. Gynec. Obst. **49** 150, 1929

Although only fifty cases of this type of ovarian tumors are recorded in the literature, the author regards them as occurring more frequently than this in that of twenty-one dermoids there were six in which there was thyroid tissue. In the three discussed in this article they were all very large cystic new growths that were filled by clear, light yellow fluid. In the wall of the cysts were typical dermoid tumors that contained cystic thyroid tissue. Chemical examination of the fluid in the tumors showed that it was free from iodine, glycogen and pseudo-mucinous material. Therefore, he denies Bauer's assumption that cases of struma ovarii are really pseudomucinous cysts. In one patient, after the removal of the tumor, the cardiac rhythm became normal and the fine tremor of the fingers disappeared.

RICHARD A. LIFVENDAHL

THE STAINING OF MALIGNANT TUMORS WITH TRYPAN BLUE R. J. LUDFORD, Proc. Roy. Soc. **104B** 493, 1929

Injections of trypan blue in sufficiently high concentration to bring about an intense staining of the fibroblasts and histiocytes of the connective tissues do not result in a coloration of the actively growing sarcoma cells of tumor-bearing mice.

ARTHUR LOCKE

THE MITOGENETIC RADIATION OF CANCER M. KISLIAK-STATKOWITSCH, Ztschr. f. Krebsforsch. **29** 214, 1929

That the mitogenetic radiation of cancerous tissue is not due to glycolysis the writer shows by the fact that it is manifested by necrotic tissue. In freshly removed material it is manifested by the cellular portions, after twenty-four hours' incubation the effect is transferred to the fluid portions. He ascribes its origin to proteolysis, which, since it is not inhibited by the addition of potassium cyanide, is of anaerobic character.

H. E. EGGERS

THE MITOGENETIC RADIATION OF CANCER A. GURWITSCH and L. GURWITSCH, Ztschr. f. Krebsforsch. **29** 220, 1929

While the mitogenetic radiation of cancerous tissues is in all probability due in large part to proteolysis, it is probable that glycolysis plays a part in its development, since in fresh living tissue the effect is shown only in the presence of dextrose. Too little is as yet known of the phenomenon to warrant an opinion of its rôle in the biology of tumors.

H. E. EGGERS

CARCINOMA OF THE BILE PASSAGES IN DISTOMIASIS OF CATS H. J. M. HOOGLAND, Ztschr. f. Krebsforsch. **29** 239, 1929

There are reported four cases of carcinoma of the bile tracts in cats infected with *Opisthorchus felinum* with a fifth case in which cancerous changes were found only on microscopic examination. Intermediate stages between the proliferative growth determined by the parasite and the cancerous growth were to be observed.

in three of the cases. The author is inclined to explain the cancer-producing action of the parasite as due to the liberation of carcinogenetic intoxicants.

H. E. EGGER

EXPERIMENTALLY INDUCED HEPATIC CIRRHOSIS IN RABBITS. G. DOMAGK, *Ztschr. f. Krebsforsch.* **29** 302, 1929.

In six of ten rabbits a diffuse hepatic cirrhosis, apparently secondary to degenerative changes in the liver, followed continued application of coal tar to the ear. There was associated splenic atrophy. None of the animals developed true cancer.

H. E. EGGER

COLICAL CARCINOMA IN A 14 YEAR OLD GIRL. D. M. CHAJUIN, *Ztschr. f. Krebsforsch.* **29** 389, 1929.

A case of adenocarcinoma of the cecum in a girl, aged 14, is here reported. The diagnosis was made only on histologic examination of autopsy material; the clinical diagnosis was intestinal tuberculosis.

H. E. EGGER

Medicolegal Pathology

POISONOUS ACTION OF INHALED ETHYL BROMIDE ON GUINEA PIGS. C. P. WAITE and W. P. YANT, *Pub. Health Rep.*, **43** 2276, 1928.

Acute hyperemia and edema of the lungs were produced with high concentration (18 per cent), the animals dying within twenty-four hours. With a concentration of from 0.32 to 2.4 per cent and exudate of plasma and a few red blood cells occurred in Bowman's capsules about the glomeruli and in the renal tubules. When the animals survived no serious damage was found in the lungs or kidneys.

E. R. LECOUNT

DETERMINATION OF THE COEFFICIENT OF POISONING WITH CARBON MONOXIDE FROM DECOMPOSED BLOOD. C. SIMONIN, *Ann. de med. leg.* **9** 11, 1929.

This coefficient is a measure of the degree of intoxication suggested by V. Balthazard and M. Nicloux (*Coefficient d'empoisonnement dans l'intoxication mortelle oxycarbonique chez l'homme*, *Compt. rend. Acad. d. sc.* **152** 1787, 1911). It is obtained by dividing the percentage of carbon monoxide per hundred cubic millimeters bound to hemoglobin in the blood under examination by the percentage such blood will contain per hundred cubic millimeters when the hemoglobin in it is saturated. In short, it is a way of stating just how near the hemoglobin of any particular person or other animal came to being saturated with carbon monoxide by that poisoning. The degree of saturation is sometimes quite high. For example, in four persons killed by this gas in a burning building the coefficient ran 0.77, 0.87, 0.89 and 0.85, respectively. In the case reported by Simonin, the coefficient was 0.77. The blood came from the body of a young man found dead in the cellar of a hotel in Strassburg. The gas came from a water heater. Because he was seen, so it was said, five minutes before, the landlord claimed that death must have been caused by natural causes. The body was examined sometime after death, and hydrogen and methane were found in the blood with the carbon monoxide; no disease was found.

E. R. LECOUNT

HISTOLOGIC DOXIMASIA OF CARBONIZED LUNGS. J. OLBRICHT, *Ann. de med. leg.* **9** 48, 1929.

A mother put her illegitimate child into a stove when it was born and burned the body so that some parts were altogether and others partly destroyed. She said that it was premature and that she had miscarried. Measurements of the epiphyseal center of ossification of the femurs, however, proved that birth had

taken place at term. Many of the viscera had escaped the flames. The kidneys, liver and spleen were the proper size for birth at term. The lungs, charred outside for a depth of from 2 to 7 mm, were carefully studied to see whether the child was born alive. Control lungs of nineteen fetuses were used, some human, others bovine and some of infants born alive. These lungs were also burned to duplicate as closely as possible the conditions of the lungs of the body found in the stove. It was learned that heat produces a rarefaction of the outer parts of lungs which may easily lead to the error of believing that the spaces found are a result of live birth and breathing. Since the lungs are not distended in all their parts by breathing for some time after birth, it was learned that burning may destroy the parts distended by inspired air and leave other parts never yet ventilated so intact that a wrong conclusion, that the lungs are those of a stillborn child, is easily possible. Consequently, Olbrycht, whose work was at the Medicolegal Institute of the Jagellonian University in Cracow, is pessimistic about the value of studying such lungs microscopically.

E R LeCOUNT

POISONING WITH WHITE HELLEBORE P M WROBLEWSKY, *Ann de med leg* 9 57, 1929

Stomach trouble is generally blamed for death among rustic and barbarous people when poisoning occurs from the empiric use of herbs to which they are still accustomed. In Caucasia and Ukraina parts of the white hellebore plant are eaten with asparagus, and to promote secretion from mucous membranes and obtain its sternutatory effect a powder from the drug is scattered about in dwellings. As an adulterant, it is employed to increase the value of inferior tobacco. It is said to cause purulent otitis media when used in the last two ways. In these countries, it is also used as a decoction from the root for chronic heart disease and to produce abortions. Cases are also reported of poisoning with white hellebore intentionally induced in order to simulate heart disease. Two deaths were investigated at the Medicolegal Institute in Kharkof (Charkow), Ukraina, where Wroblewsky is Chief. The victims were both women who had taken a secret remedy, the one for heart disease, the other to bring on abortion. Both women died on the day that they were poisoned. The alkaloids of veratrin were readily found, and extracts of the viscera produced characteristic pharmacologic reactions in frogs and rabbits.

E R LeCOUNT

BARBITAL POISONING P MULLER, *Ann de med leg* 9 72, 1929

Idiosyncrasy was the explanation offered for the severe poisoning, a coma for about twenty-four hours, following two doses of 0.75 Gm of barbital taken four hours apart with suicidal intent. In discussing the report of Muller, Kohn-Abrest emphasized the danger of the preparations of barbituric acid when taken by persons with renal or hepatic disease. He also urged that the patient's tolerance should be tested carefully before any of these hypnotics are prescribed in other than small doses. When renal disease is present, there is likely to be nausea and vomiting, and intolerance is indicated by an intoxication resembling that of alcohol.

E R LeCOUNT

NEW LAWS IN FRANCE PERTAINING TO DEAD HUMAN BODIES DUVOIR, *Ann de méd leg* 9 77, 1929

A new decree was signed by the Minister of the Interior and of Labor in March, 1928. The Act is in seven sections and was enacted chiefly to bring into accord various regulations previously in force. Section 1 is concerned with burial, section 2 with the transportation of bodies, and supplementing previous regulations are matters pertaining to hygiene, the use of disinfectants and the hermetical sealing of caskets, section 3 deals with exhumations. The previous obligatory attendance of a physician is abolished. Section 4 pertains to cremation. Certificates are

required from the attending physician and from a physician who is also a public official, regarding the cause of death before cremation can be carried out. In case these are not obtained an inquiry concerning the cause of death starts automatically. No authorization for cremation can be given unless the cause for death is a natural one. Section 5 consists of regulations for embalming and for this also a certificate from a physician is required setting forth that death resulted from natural causes. The use of arsenic, mercury and lead in embalming fluids is forbidden, and the methods of embalming are prescribed. Section 6 states under what conditions postmortem examinations may be performed and casts and death masks made from dead bodies. The provisions of this part of the decree require an interval between death and postmortem examinations made in private homes and does not affect the considerable freedom with which such examinations are made in hospitals. This interval seems too long when compared with practices in some other countries. In Section 7 supervision of the proceedings carried out with dead bodies is provided for, representation at embalming and postmortem examinations to prevent crime being hidden by, for example, removal of the uterus of women dead from abortion, of organs injured by bullets, etc.

The decree as a whole is not concerned with postmortem examinations conducted under military regulations. Since the previous decree of February, 1842, the right of hospital authorities to proceed with postmortem examinations has been recognized, and efforts to continue this practice have enjoyed thorough cooperation of the municipal and other officials who have recognized the interests of public health and medical science in postmortem examinations.

E R LECOUNT

THE SIGNIFICANCE OF TATTOO MARKS COUREAUD, *Ann de med leg* 9 100, 1929

A careful study was made of the different designs, inscriptions, etc., tattooed on 300 men serving as marines in the French navy, both recruits and volunteers. It was found that tattoo marks had undergone a change, former depictions of events in mythology or in some chimerical romance long entrenched in the affections of the people were no longer employed as heretofore. The former delicately executed and artistic representations in many colors were replaced by coarse work of a low order. Consequently former complicated classifications were replaced by grouping them into only two classes. The first group was made up of emblems useful solely for identification and consisted of representations of anchors, buoys and other objects with which the marines were occupied daily, also figures referring to events such as bombardments, battles, places visited ashore, a dragon for the Orient, an oasis with palms, etc., and with these there were often dates. The marks of this group were often small and many were located on the back of the hand between the metacarpal bones of the thumb and index finger.

A second and much larger group of tattooings was made up of a great variety of designs of much greater medicolegal value. They indicated questionable morality or were definite insignia of sexual perversion, of secret societies, communistic affiliations, rebellion against or hate of discipline, etc. The "jackies" decorated with marks of this sort usually possessed records of punishment for infractions of regulations, or for graver offenses.

E R LECOUNT

ACCIDENT AND OSTEOSARCOMA QUENEZ and MULLER, *Ann de méd leg* 9 122, 1929

A laborer unloading slag with a wagon fell about 9½ feet twisting his right knee but without any direct violence to the part. Swelling began almost at once and this was followed by pain and a thickening of the periosteum below the patella in the tibia where the terminal tendon of the muscularis quadriceps femoris is inserted. It was thought that the periosteum there possibly was torn when the accident occurred. The symptoms and disability continued until almost a year later when by incision osteosarcoma was recognized. The authors believe that the

conditions observed fulfil all those which were agreed at the Congress of Legal Medicine in France in 1925 should be met to predicate successfully causal relation between accident and tumor

E R LECOUNT

PROLONGED INTRATHORACIC RESIDENCE OF A FRAGMENT OF AN ARTILLERY
SHELL TREVEL, Ann de med leg 9 125, 1929

This account has the following unusual features The foreign body was not found until seven years after the injury, repeated attacks of hemoptysis caused the incorrect diagnosis of pulmonary tuberculosis, an unsuccessful attempt was made to remove the fragment nine years after the wound was received, the piece of metal was still there close to the root of the right lung as late as August, 1927, and there had been many revisions of war pension due to changes of incapacity

When the injury was received, it was not expected that the man would live The soft tissues including most of the muscles about the right pectoral and scapular regions and right shoulder were either shot away or subsequently removed, and the right side of the trunk, right arm and thigh were also severely injured

E R LECOUNT

ACCIDENTAL POISONING WITH HYDROCYANIC ACID GAS E KOHN-ABREST,
Ann de med leg 9 132, 1929

Nine deaths are reported of persons who entered places still incompletely ventilated after hydrocyanic gas had been used as an insecticide The bodies were examined at different times after death one after four, five after eight, one after eleven and two after fifteen days had elapsed No trace of the poison was found in two of the bodies, one of these persons had died four days and the other eight days previous to the examination In the remaining seven, traces of the poison were found, but free hydrocyanic acid was found in only one body examination was made eleven days after death After disinfection with the gas traces imperceptible to smell and nevertheless highly dangerous may remain Its use should be surrounded with strict precautions and regulations

E R LECOUNT

CARBON MONOXIDE POISONING IN A COLIERIA B WEISSBERGER, Wien Klin
Wchnschr 40 1605, 1927

During about eleven months of the year 1925, illness of sixteen laborers in a coal mine was noted and great perplexity over its nature resulted because by daily analysis of the air in the mine no carbon monoxide was found The symptoms were of two kinds, hemorrhages and trouble with the nervous system They exhibited a great variety the hemorrhages were in the subcutaneous tissues, retinas or stomach, not all of them in each patient, however Likewise the nervous symptoms of headaches, monoplegias, hemiplegias, speech paralysis, cardiac neurosis, hyperesthesia, paresthesia and insomnia were met with in different laborers, increased blood pressure and general weakness were also observed

Three of the sixteen died, and two postmortem examinations were obtained In one body, there were multiple hemorrhages in the spinal cord and brain with considerable blood in the fourth ventricle, the man, aged 44, died rather soon after the onset of symptoms The other body was that of a man, aged 29, whose illness lasted for about a year Following eight or ten days of headaches, a right hemiplegia developed When this stroke came on his blood pressure was 185 There is no mention of any prolonged somnolence or coma such as occurs with acute carbon monoxide poisoning, yet when he died about a year after the stroke, softenings were found in each globus pallidus

These changes in the brain, perhaps more than any other evidence, led to the conjecture that the complaints of all sixteen were due to carbon monoxide There had been an explosion in the mine in 1924, and it was thought that the

carbon monoxide from that was adsorbed by dust and subsequently poisoned the miners. No tests of the blood were made. All the miners wore gas masks.

E. R. LeCount

ACCIDENTAL POISONING WITH HYDROCYANIC ACID GAS M. KAISER, Wien
klin Wchnschr 41 958 1928

Prussic acid gas is extensively used in Austria to kill insects in houses. It is successful. It kills roaches, lice, bed-bugs, moths, beetles, mites, etc., although some may require a second disinfection. Bedding, clothing, rugs, fur and other materials used in households may retain the gas by absorption. Consequently, if the disinfection is done in cold weather, it is necessary to warm such goods or the rooms containing them to drive off the gas.

Two deaths and the poisoning of eight others who recovered resulted from failure to take such measures when household equipment was moved after disinfection to new homes in the winter. The warmth of the bodies of those who were poisoned released the gas, so it is stated. Three other deaths in Austria from the use of this insecticide are also mentioned, all however, in other ways. The total space disinfected in 1927 was equal to 196,373 cubic meters or a region about 190 feet in each of its three dimensions.

E. R. LeCount

INTERNAL LESIONS IN ELECTROCUTION P. SCHNEIDER, Wien med Wchnschr
79 53, 1929

In a power plant a man was electrocuted by a current of 5,000 volts, he gave one cry, fell and was then apparently dead. For one hour attempts were made to resuscitate him and during this time spinal fluid was withdrawn. The fluid came away in a stream under a pressure estimated as equal to 300 cmm of water. At the postmortem examination made two days after death, a few small subendocardial hemorrhages, considerable epidural spinal hemorrhage about the needle wound and an edema of the brain were found, and these, with the conditions encountered when the spinal fluid was withdrawn were altogether regarded as evidence that the heart had continued to beat for some time after the shock was received. Consequently, death was explained by effects that the current had on the central nervous system. There is no mention of any microscopic examination. If this had been done and very marked alterations had been found in the myocardium, death under the conditions related might be explained by defective blood supply to higher nerve centers. The current entered the palm of the right hand and passed out the sole of the right foot.

E. R. LeCount

A THALAMIC SYMPTOM-COMPLEX FROM FORMALDEHYDE POISONING A.
WEGER, Ztschr f d ges Neurol u Psychiat 111 370, 1927

In Charvok (Kharkof), Ukraine, both formaldehyde and phenol escape as vapors in the manufacture of bakelite from a natural product "Rigilite." Practically all the employees were found affected by the formaldehyde gas with which the air was saturated in compartments they were required to enter or in which they remained for varying periods. The symptoms were a general malaise, increased susceptibility to temperature changes, dizziness and severe headaches, a difference in the temperature of the two lateral halves of the body, abnormalities of sweating, disturbances of the temperature of and sensation in the skin, of the two lateral halves of the body and dysesthesia, algesia and hemialgesia.

No opportunity was had to examine the central nervous system but it is suggested that these remarkable clinical manifestations were caused by disturbances in the optic thalamus, hypothalamus and especially the tuber cinereum. The left thalamus was more often involved than the right. Presumably these parts of the brain have special chemical relations with the poison or poisons which are not possessed by other parts. The investigators believe that formaldehyde is more

to blaine than phenol. New investigations are promised, and building modifications to secure satisfactory ventilation and prevent future similar poisonings were instituted.

E R LECOUNT

Technical

SILVER STAINING OF THE SKIN AND OF ITS TUMORS GEORGE F LAIDLAW,
Am J Path 5 239, 1929

Long known as a capricious staining substance, silver does not always deserve this reputation. Provided that certain conditions are fulfilled, silver staining becomes as simple and as certain as the staining of nuclei with hematoxylin, at least, this is true of the peripheral nervous system, of the skin and of the argyrophil reticula generally. The conditions are suitable fixation, suitable mordanting and the use of silver solutions from ten to twenty times stronger than those in vogue. The fixative determines the result of the stain. When the silver worker has grasped this principle, half of his difficulties disappear. Differential silver staining might well be called differential fixation, for a given silver stain will produce different effects according to the fixative employed. This paper deals with the application of these principles to the skin and to tumors of the skin, the fixatives selected being Bouin's fluid and neutral formal. The resulting preparations are described separately, for these fixatives are not interchangeable.

AUTHOR'S SUMMARY

LIGHT AS A FACTOR IN THE IMPREGNATION OF BRAIN SECTIONS WITH THE AMMONIACAL SILVER SALTS NATHAN CHANDLER FOOT, Am J Path 5 365, 1929

Frozen sections of brain tissue should be shielded from light before and up to the time that they are impregnated with silver salts. Light inhibits the impregnation of the oligodendroglia and microglia with silver diamino carbonate and produces troublesome precipitates in the sections. It does not appear to influence the impregnation of the macroglia materially. It somewhat inhibits the impregnation of the cortical neurons with silver diamino hydroxide, after bromuration. This fact may be made use of by technicians desiring to suppress these cells and their dendrites and to accentuate the microglia by contrast.

AUTHOR'S SUMMARY

A METHOD FOR SECURING HUMAN OVA FROM UTERINE TUBES J P PRATT,
E ALLEN, Q U NEWELL and L J BLAND, J A M A 93 834, 1929

Two methods to obtain living ova were used. In the first method, when the tubes were not to be removed, the uterus was compressed by uterine elevating forceps applied just above the cervix. A small needle with a syringe attached was then introduced through the muscle into the cavity of the uterus. Salt solution was then injected into the cavity and allowed to run out through the tube. One tube was compressed with the fingers while the other was being washed. The fluid was collected as it ran out the fimbriated ends and was carefully searched for ova. This method is also useful to test the patency of the tubes.

In the second method, when the tubes were removed at operation they were first dissected free from the mesosalpinx. A small cannula was fixed in the fimbriated end of each tube and then washed with physiologic solution of sodium chloride. The washings were then examined for ova. Freeing of the tube seemed necessary as otherwise there might have been a kinking which would have interfered with successful washing. Five undoubted ova have been recovered by the methods described.

A RAPID QUANTITATIVE PRECIPITIN TECHNIC ALAN BOYD¹ and JOSEPH G. BAIER, JR., J. Immunol. **17** 29, 1929

The measurement of volume of precipitate in the precipitin reaction has been found to be fairly simple, rapid and reliable when Van Allen thrombocytocrits are used. The technic described is recommended for the serologic study of biologic relationships where more measurements and fewer family trees are needed.

AUTHORS' SUMMARY

THE DIAGNOSIS OF NECROSIS OF THE PANCREAS BY DIASTASE DETERMINATIONS OF THE URINE J. WOHLGLMUTH, Klin. Wchnschr. **8** 1253, 1929

Titration of the diastase of the urine in a buffer-soluble starch medium at pH 7.2 has been helpful in determining necrosis of the pancreas in thirty-six of thirty-eight patients. The details of the procedure should be consulted in the original article.

EDWIN F. HIRSCH

Society Transactions

LOS ANGELES PATHOLOGICAL SOCIETY

Regular Meeting, May 14, 1929

NEWTON EVANS, *President, in the Chair*

CARCINOMA OF THE FALLOPIAN TUBE ROY W HAMMACK

The patient was a woman, aged 48, whose complaint dated from Dec 26, 1926. While sitting quietly in a chair, she suddenly had a vaginal flow of bright red fluid. For seven months, she used at least three pads daily. She never had any pain or discomfort, nor was there any loss of weight. In fact, during this period she gained several pounds. The fluid after the first time was not bloody, but clear. When she entered the hospital, examination showed a uterus of normal size with no nodules. Apparently an adnexal mass was not noted, at least there was no notation of it on the patient's chart. When the cervix was dilated, the probe met with an obstruction 1 cm from the cervical outlet, and a diagnosis of uterine fibroid was made. Laparotomy was done with a tentative diagnosis of "possible malignant growth of the body of the uterus," and this specimen was removed. The specimen is a fallopian tube and was removed intact. It looked like a hydrosalpinx, measuring 45 cm at one end, tapering to a normal size at the uterine end. The surface was smooth. When the tube was opened, a small amount of bloody fluid escaped, and the lining of the cavity was as you see it—a large number of rather soft, friable, papillary masses.

The microscopic features, as exhibited by the sections shown, include papillary epithelial structures, the composing cells showing considerable irregularity and a few mitotic figures. The nuclei are hyperchromatic. There is practically no infiltration of the wall, which is thin. It seems to be definitely malignant, though it shows little evidence of infiltration.

PULMONARY EMBOLISM FOLLOWING HIBBS' FUSION OPERATION ROY W HAMMACK

The history of this case briefly was that of a young man about 32 years of age. Last November, he was carrying a large block of ice, and on letting down the load hurt his back. The pain persisted, and x-ray studies showed what was called a "slight slipping of one of the lumbar vertebrae." On April 1, a Hibbs fusion of the third, fourth and fifth lumbar vertebrae was done. This operation and the convalescence were apparently uneventful until April 19, when the patient had a rather sudden rise in pulse and temperature. Examination at that time showed some pulmonary physical signs which were interpreted as bronchopneumonia. From that time on, the patient had mild persistent pulmonary signs, until on May 5, after he had apparently been improving, he suddenly became cyanotic and dyspneic, and died within about twenty minutes. Autopsy showed bilateral pulmonary thrombosis with infarctions of the lungs. The site of the operation on the lower vertebrae was investigated and nothing unusual was found there, there being no evidence of infection or thrombosis. It was a coroner's case. There were thrombi of different ages in the lung, presumably having their origin at the site of operation. No other origin of emboli could be demonstrated at autopsy. The first symptoms, which followed operation by about two and one-half weeks, were possibly due to the lodging of the first emboli.

BUERGER'S DISEASE REPORT OF A CASE ROY W. HAMMACK

The patient a man aged 45, thought that he had injured his leg. The first evidence of trouble was a hard nodule in the course of one of the veins in his leg in July 1928. Later, another lump appeared in another vein. It was evidently a migratory phlebitis, a rather characteristic sign of Buerger's disease. The phlebitis progressed and the patient entered the hospital in September. At that time he had some slight discoloration and a little tenderness in his toes. He did not have symptoms of occlusion, except that he had a little pain in the right and left calf muscles when he walked any considerable distance. A tentative diagnosis of Buerger's disease was made and a piece of thrombosed vein was removed for microscopic examination. A thrombophlebitis, fairly characteristic of the disease, was demonstrated. In April, the patient's toes began to become discolored with more marked pain. He received one intravenous injection of typhoid vaccine and subsequently a number of injections of salt solution and Ringer's solution but without any effect. His circulation became rapidly poorer, resulting in gangrene of the great toe. In spite of no visible evidence of disease of the leg other than an absence of pulsation of the arteries, a high amputation of the leg was done. The popliteal artery was found occluded at the point of amputation. Gangrene of the great toe and a gangrenous spot at the base of the fourth toe was observed on the amputated member.

The sections of the vein secured at biopsy were fairly characteristic. They showed an inflammatory lesion of the vessel wall with a thrombus in varying states of organization, with considerable round cell and some leukocytic infiltration. The presence of giant cells seemed rather characteristic. The lesion in the bit of vein removed before amputation seemed to be sufficiently characteristic to make certain diagnosis of obliterating thrombophlebitis, or Buerger's disease. Microscopic section showed fibrin in the center with more or less necrosis, and at the edge of the fibrin there were many infiltrating round cells. There was a beginning canalization and in one of the sections at the margin of the fibrin among the round cells there were one or two giant cells. Throughout the wall of the vessel there were a good many round cells and occasional leukocytes.

The popliteal artery from the leg showed the wrinkled remainder of the lining of the vessel. There was a little area of calcification in the wall but the whole lumen was filled with an organized thrombus, and canalization of the thrombus had taken place. Near the center of the thrombus there were brown areas of blood pigment. The irregular intima was well preserved. As Buerger claimed it seemed to be a thrombotic process followed by the organization of the thrombus and finally more or less recanalization. It is accompanied by more or less acute inflammation.

RUPTURED PAPILLARY MUSCLE OF THE HEART R. M. CRUMRINE

The patient was a white man, aged 51. He was sent into the hospital with a diagnosis of "acute abdomen." On the day before admission, he had driven 60 miles in a car and had become very ill thereafter with pain which originated behind the sternum and radiated toward the umbilicus, and which was relieved by frequent vomiting. There was no pain in the shoulders or the arms. He had had similar abdominal pain two weeks before, and this had persisted more or less ever since. The patient was a cement worker, and his past health had been good.

He was admitted as having an acute abdominal condition, and a surgical consultant was called. The latter, however, diagnosed it as "acute cardiac failure, probably due to coronary disease." The surgical resident who made this diagnosis stated that the liver was enlarged almost to the umbilicus and was tender. He believed it to be a plain case of cardiac failure with cyanosis of rather peculiar distribution involving only the head and shoulders. The heart sounds were distant, and a systolic apical murmur was present. Several attempts to obtain the blood pressure were unsuccessful. The patient died thirty-six hours after admission.

and at autopsy the abdominal cavity showed no peritonitis or other evidence of acute abdominal disease. The liver weighed 2,300 Gm, and the cut surface showed a definite nutmeg appearance. The heart weighed 450 Gm and presented a complete rupture of one of the larger papillary muscles of the mitral valve. The torn surfaces showed considerable pinkish exudate. The coronary arteries were both markedly sclerosed, and there were large areas of fibrosis visible in the wall of the left ventricle. The aortic valve was normal, and the entire aorta showed only slight atheroma. Microscopic sections substantiated the opinion that the muscle was ruptured at a time probably two or three days before death. They also showed marked fibrous scarring of the papillary muscle and in the ventricular wall.

It is usually stated that ruptures follow acute or chronic occlusion of the left coronary, which is the sole blood supply of one of the papillary muscles of the mitral valve. Occlusion of other branches of the coronaries doubtless would contribute to fibrosis and rupture of other papillary muscles.

HEMORRHAGE INTO THE SUPRARENAL GLAND IN AN INFANT R. M. CRUMRINE

A 22 days old infant had hemorrhagic disease of the new-born and infection of the umbilical cord. The condition cleared up after one or two intramuscular injections of whole blood, but a peritonitis developed secondary to the infection in the umbilical cord. A mass was palpated in the right upper quadrant.

At autopsy, a resolving peritonitis was found. The mass in the right upper quadrant proved to be a hemorrhage into the suprarenal gland. The gland was nearly as large as a prune with hemorrhage extending under the renal capsule and forming a small mass at the lower pole of the kidney. The opposite kidney and suprarenal gland were normal. Microscopic sections showed a normal suprarenal cortex with hemorrhage into the medullary portion, a picture suggestive of infarction.

The temperature in this case was not extremely elevated as is the case usually. The highest recorded temperature was 103 F.

TOXIC HEMORRHAGIC HEPATITIS REPORT OF CASE HOWARD A. BALL

A male child, 21 months of age, for ten months had had a chronic skin condition, diagnosed as eczema. The child entered the hospital with an infection of the upper part of the respiratory tract, which had been present for about one week. Until this time, he had been considered by his mother to be perfectly well. He was a full term child and was instrumentally delivered, he was never breast fed.

Examination revealed that the face was covered with crusting lesions and that there was a similar condition of the skin of the body. Roughened breath sounds and rales throughout the lungs were the only other positive observations. A white blood cell count was 10,300 per cubic millimeter, with a differential count of 80 per cent polymorphonuclear and 20 per cent mononuclear cells. The blood Wassermann reaction and the urinalysis were negative. There was no roentgenographic evidence of bronchopneumonia.

The child's general condition was considered good until five days after admission. The skin lesions on the body had completely healed. The child suddenly became ill and had what was described as a "waxy pallor." At this time, the red blood cell count was found to be 3,000,000 and the hemoglobin 50 per cent (Tallquist), few platelets being found in the smear. Because of the evident anemia and the weakened condition of the patient, a transfusion was proposed. The child succumbed before it could be started.

Examination of the body fifteen hours post mortem revealed a well developed and well nourished male child, with a stated age of 1 year and 9 months. Over the face were numerous pitted, granulating areas, some of which were round and punched out and others confluent giving a serpiginous outline. Anterior to the right ear was an area of exuding skin. A similar area was present on the

anterior aspect of the neck. There were also a few punched-out areas on the right wrist and one on the extensor surface of the left forearm. Within the areas of postmortem livor could be seen darker colored patches of scaly skin, slightly raised above the surrounding surface. The lungs and heart showed no evidence of pathologic change.

The liver was large and markedly softened, and beneath the capsule could be seen mottled areas of yellow and red, somewhat simulating a patchy ecchymosis.



Fig 1—Gross appearance of cut surface of liver, showing numerous hemorrhagic areas, resembling a diffuse cavernous hemangioma. Microscopic examination reveals a liver necrosis and extensive areas of hemorrhage.

Cut section revealed throughout the entire liver substance areas of hemorrhage, not definitely circumscribed, some of which were firm and appeared as thromboses, the whole picture roughly resembling a large and diffuse cavernous hemangioma. Less than one third of the liver substance was uninvolved. The tissue was friable.

The spleen was small and somewhat mottled, its cut section not showing any prominent malpighian corpuscles. The kidneys were normal in size and were

definitely anemic. The cortex showed some cloudy swelling, and a slight icteric tinge. The bladder was normal. The mesenteric lymph nodes were swollen, but the intestine was without gross evidence of pathologic change. The bone-marrow showed no gross change.

Smears from the lesion anterior to the right ear showed numerous gram-positive cocci arranged as staphylococci. Smears from the liver showed no organisms, but much fibrin and cellular debris.

Microscopic sections of the skin lesions showed a picture consistent with impetigo, gram-positive cocci were demonstrated at the base of the ulcerated area. Sections of mesenteric lymph nodes showed congestion, but no hemorrhage, and Gram-Weigert stains revealed no organisms. Sections of the liver (fig. 2) showed large and small areas of fibrin, within which were enmeshed many red and white blood cells in apparently normal proportions. Areas of early necrosis of the liver substance were present. Gram-Weigert stains revealed no organisms. Sections of spleen showed a tendency to formation of hemorrhagic



Fig. 2—Photomicrograph showing areas of fibrin and enmeshed blood cells, and at the left, normal-appearing liver substance.

areas, being in this respect somewhat similar to the liver. Smears of the bone-marrow stained with Wright's stain showed no recognizable abnormality.

For want of a term more suitable we have called this toxic hemorrhagic hepatitis cause undetermined. Whether or not it is an expression of a purpuric tendency, I am not prepared to say.

PRIMARY CARCINOMA OF LIVER, WITH FATAL HEMORRHAGE THROUGH THE COMMON BILE DUCT. HOWARD A. BALL

This case of primary carcinoma of the liver is rather unique because of the mode of death.

A Mexican, aged 47, who had complained of "indigestion" for many years, entered the hospital, Jan. 22, 1929, with the complaint of bleeding from the stomach of two days' duration. The first blood vomited was bright red, and that of the next day was of coffee-ground character.

Examination showed a patient in rather poor condition. The pulse was weak, the rate 80 per minute. The blood pressure was 100 systolic and 55 diastolic. The results of the examination were otherwise unimportant. The urinalysis showed nothing of note. The blood count showed 3,610,000 red blood cells per cubic millimeter, with hemoglobin (Sahli) 70 per cent, white cells 9,800 per cubic millimeter, with polymorphonuclears 79 per cent and mononuclears 21 per cent. A diagnosis of bleeding peptic ulcer was made, and the patient was given a transfusion of 450 cc whole blood of the same type after a cross-agglutination test was negative. The patient died eighteen hours after entrance.

Autopsy was performed twelve hours after death. The only observations of note were in the liver and gastro-intestinal tract. The liver was of average size, but nodular over the surface, individual nodules averaging about 7 mm in diameter, the typical picture of atrophic cirrhosis. There was fibrosis surrounding these nodular areas, and some variation in color, the major portion of the liver having the usual brownish color, but situated on the anterosuperior surface of the liver on the right side was a raised area measuring 8 by 8 cm, which was less nodular and light gray to yellow, and which was friable. This was later proved to be carcinomatous tissue. Situated in the porta, just above the junction of the cystic and hepatic ducts, was a necrotic mass of tissue, soft and fluctuant, which was found on gross section to consist of necrotic tissue with fluid and clotted blood. One hepatic duct was found connecting with this necrotic mass. This, as well as the common bile duct, contained necrotic tissue and clotted blood. The stomach and the small intestine contained at least a liter and a half (1,500 cc) of partially digested bloody fluid, and it seemed evident that death was due to hemorrhage through the common bile duct. No esophageal or pyloric varices were present.

Cut section of the liver revealed tumor thrombi in many branches of the portal vein, but the exact point of communication between the portal system and the necrotic mass described was not demonstrated.

Microscopic sections of liver showed an active interstitial hepatitis, with numerous small round cells in the connective tissue, and a primary carcinoma of the liver cell type.

Fox and Bartels in a review of the English literature published since 1901 (ARCHIVES OF PATHOLOGY, August 1928), collected eighty reports of cases of primary carcinoma of the liver but made little note of the almost constant association with atrophic cirrhosis.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Oct 10, 1929

J HAROLD AUSTIN, *Presiding*

ACTION OF WHOLE FRESH BLOOD ON PNEUMOCOCCI MYER SOLIS-COHEN and RACHEL ASH

The present studies continue work previously reported by Heist and Solis-Cohen in which a capillary tube method was used to investigate and measure the bactericidal properties of whole fresh blood. In the present work, virulent strains of pneumococci were implanted in human blood of known resistance to such organisms. By making frequent subcultures from such capillary clots to the surface of blood agar slants, an actual diminution in number of colonies could be demonstrated, thus adding weight to the theory that pneumococci are destroyed in such blood. In an attempt to dissociate the influence of leukocytes from that of plasma, we made microscopic studies on clots centrifugated before coagulation had taken place. We found that growth of pneumococci occurred in the plasma

layer of such centrifugated clots before organisms could be observed in the leukocyte layer or in the usual Heist smear. Inhibitory action of whole blood against pneumococci would thus seem to be dependent on the action of leukocytes. In a centrifugated clot seeded with large numbers of pneumococci, emigration into the plasma is inhibited, whereas when few organisms are present leukocytes are attracted to the area of growth.

INTERMUSCULAR LIPOMAS REPORT OF THREE CASES MOSIS BEHREND

Greater care should be taken in the classification of these tumors. The overlapping of the terms intramuscular and intermuscular should be avoided. This can be done by a stricter analysis of the anatomic arrangement of these tumors. Some grow between the muscles, while others originate in the muscle. All our cases were of the intermuscular variety, which are rather more common than the intramuscular type. In either case, these tumors are rare.

Pure lipomas only should be included and not those of fibrous and fatty type, as has been done by some authors.

Lipomas growing between or within the muscle may occur in any part of the body. They are usually found in the extremities, a common place being the region of the trapezius muscle.

The symptoms of lipomas are those of benign tumors, depending on the size and location.

The differential diagnosis is of some importance and is difficult to make. Lipomas may be mistaken for angiomas, sarcomas or muscle tuberculosis. An exploratory puncture withdrawing some fatty material will always confirm the diagnosis. Examination by means of the x-ray will help in separating sarcoma from lipoma. One specimen was received from the anatomie laboratory of the Jefferson Hospital, the first ever noted by Prof. J. Parsons Schaeffer in an experience covering twenty-five years. The lipoma was under the trapezius muscle. The other two specimens were obtained from patients in my service in the Jewish Hospital. In one case, in a colored man, the tumor was under the trapezius muscle, while in the second case, in a woman, the lipoma was beneath the rectus femoris muscle.

In all, 190 cases have been reported, exclusive of the cases mentioned in this synopsis.

This paper with complete bibliography is published in full in *The American Journal of Surgery*.

PRIMARY SQUAMOUS CELL CARCINOMA OF THE VAGINA IN PATIENT 16 YEARS OLD AND SIX MONTHS PREGNANT LOUIS TUFT

This paper will be published in full in a later issue.

THE NEW BUREAU FOR THE STUDY OF TUMORS JOSEPH MCFARLAND

An abstract of this paper has been published in the ARCHIVES (8 837 [Nov.] 1929).

DEMONSTRATION OF AN INSTRUMENT FOR DETERMINING THE COAGULATION TIME OF THE BLOOD GEORGE M. DORRANCE

This simplified method of obtaining the coagulation time of the blood was first introduced to the medical profession sixteen years ago by Dr. G. M. Dorrance.

The present improved instrument consists of a rectangular glass container measuring 6½ inches (16.5 cm) in length, 1½ inches (3.8 cm) in width and 4 inches (10.16 cm) in height. A bakelite cover with eight openings through which seven glass rods and a thermometer are inserted completes the instrument.

The principle of the test is to determine how long a time must elapse for clotting to occur in a drop of blood placed on the end of a glass rod (at body temperature).

Technic—The container is half filled with water at a temperature of 99 F, the cover is replaced and the rods allowed to remain immersed for half a minute the cover is removed the rods dried and drawn upward so that when the cover is reapplied their tips are about one quarter of an inch (0.61 cm) above the water

The finger of the patient is prepared and given a smart prick with a needle, the first drop of blood is mopped away, then an even film of blood is placed on the tip of each rod, care being taken to avoid touching the skin with the rod or allowing blood to touch the sides of the rod At stated intervals of time, the rods are immersed in the water, and the time when clotting begins and ends is noted by the character of the precipitate When the rods have been immersed, the cover is removed and the type of clot can be seen by holding the rods to the light, the tips are next gently mopped off on a clean towel and the texture and character of the clot examined

In this instrument the normal clotting time is between five and eight minutes

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Nov. 11, 1929

HENRY C SWEANY, *President in the Chair*

PRIMARY CARCINOMA OF THE LUNG FOLLOWING TRAUMA H GIDEON WELIS

This article will be published in full in a later issue of the ARCHIVES

DISCUSSION

EDWIN F HIRSCH The relation of trauma to malignant growths is noted especially well in the distal parts of the extremities where for example, following a bruise, fibrosarcomas appear, such as Harbitz has described in the ARCHIVES OF PATHOLOGY

THE EFFECT OF EXPERIMENTAL HYPERTHYROIDISM AND OF INANITION ON THE HEART, LIVER AND KIDNEYS J P SIMONDS and W W BRANDES

This article appears in full in this issue p 445

DISCUSSION

GEORGES M CURTIS In view of the results obtained by Dr Simonds and Dr Brandes it is of interest to recall the work of one of Asher's pupils Rohrer (*Biochem Ztschr* **145** 154, 1924), using a modified Krogh microspirometer, studied the oxygen consumption of surviving tissues He first determined the volume of oxygen consumed by weighed bits of muscle liver and kidney taken from normal control white mice Other mice were then fed thyroid extract and the determinations repeated In the resulting hyperthyroid state, muscle consumed 24 per cent more oxygen liver 23 per cent and kidney but 16 per cent more than the normal organ The increase in oxygen consumption for the entire animal was not given In white rats, this is about 37 per cent (Curtis *Biochem Ztschr* **167** 321 1926) Feeding of thyroid extract increases the oxygen consumption of surviving organs in varying degrees These results may throw some light on the varying weight loss of organs in experimental hyperthyroidism

LEUKOPLAKIA OF THE STOMACH HARRY A SINGER

This article will be published in full in a later issue of the ARCHIVES

THE INFLUENCE OF BLOCKADE OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE
FORMATION OF ANTIBODIES PAUL R CANNON, RAYMOND B BAER, F L
SULLIVAN and J R WEBSTER

Metchnikoff's idea that antibodies are products of the parenteral ingestion and digestion of foreign substances by phagocytic cells, has received additional support within recent years as a result of the interest in the functions of the so-called reticulo-endothelial system. According to the hypothesis of Metchnikoff, if phagocytosis and intracellular digestion of foreign materials could be prevented, antibody formation would also be prevented. Blockade of the phagocytic cells would seem to furnish a good method for the elucidation of the problem, but the results of such experiments have been inconclusive, some investigators having found a decrease in antibody formation subsequent to the so-called blockade, some an increase and others no effect at all. A close analysis of their work, however, reveals the probable causes of these divergent observations.

It is obvious that the blockade by particulate matter of every reticulo-endothelial cell of the mammalian body would be extremely difficult, and, indeed, is probably impossible. Even if it were possible, the adaptive powers of the body would soon furnish more phagocytic cells, either by further regeneration, or by differentiation of forms previously inactive. It is useless to expect complete blockade. Nevertheless, it should be possible to eliminate a great number of the actively phagocytic cells by blocking methods and, if the hypothesis of Metchnikoff is correct, to obtain a corresponding decrease in antibody formation.

In testing this idea, however, the following conditions are essential:

- 1 A proper amount and kind of blocking material must be injected
- 2 This injection should be continued throughout the experiment
- 3 Both intravenous and intraperitoneal injections of the blocking material are necessary
- 4 A sufficient number of animals to eliminate individual variation must be used
- 5 A small dose of "test antigen" should be employed. Adequate blockade of the reticulo-endothelial system cannot be expected unless the first three of these conditions are observed, and the effects of the blockade on antibody formation cannot be clearcut unless the last two are recognized.

The experiments here described were performed with the aim in view, first to block as many of the phagocytic cells of the body as possible, and second, and of equal importance, to keep blocked these and any other cells that might regenerate or differentiate into active forms. This can be successful only if frequent intravenous, as well as intraperitoneal, injections are made. In addition, a sufficient number of animals must be used to eliminate the factor of individual variation. Even with these prerequisites it is probable that the results, as far as antibody formation is concerned, will be obscured unless the proper dosage of "test antigen" is used. This was shown by Motohashi when he demonstrated that splenectomy in the rabbit is followed by a decrease in the liberation of antibody into the blood stream only when a small amount of antigen is injected.

Thirty rabbits in all were used. The blocking material was a suspension of from 4 per cent to 8 per cent of Higgins' india ink (white label bottle) in 0.85 per cent sodium chloride solution. This was injected two or three times a day, intravenously and intraperitoneally, in amounts ranging from 5 cc to 25 cc. At the end of two weeks of such blocking procedures, 0.5 cc of a 0.5 per cent suspension of sheep's red blood corpuscles, washed five times, was injected intravenously. The sheep's cells were always from fresh blood and were centrifuged at the same speed for the same period of time during the last washing. The rabbits in each series were selected so as to be of practically the same weight, and a constant amount of antigen was injected into each animal. At intervals of time the serums, inactivated at 56 C for thirty minutes, were titrated in a system as follows: 0.2 cc of a 1 to 4 dilution of pooled guinea-pig serum, 1 cc of diluted serum and 0.5 cc of a 2.5 per cent suspension of washed sheep's corpuscles in 0.85 per cent sodium chloride solution. The highest dilution of serum causing complete hemolysis in

one hour at 37 C was taken as the titer. In series 1 and 2, the blocking procedures were discontinued at the time of injection of the "test antigen", in series 3 and 4, they were continued until the end of the experiment.

The results of these experiments may be summarized as follows:

1 The liberation into the blood stream of hemolysins to sheep's red corpuscles following blocking procedures depends on the manner of administration of the blocking material and the amount of antigen injected. Repeated injections of suspensions of India ink, particularly intravenously, and continued after the injection of a small quantity of "test antigen," are followed by a significant decrease in the liberation of antibody into the blood stream, this liberation apparently varying inversely with the extent to which the phagocytic cells are blocked.

2 This decrease in output of antibody is independent of the individual variation of the animals, of loss of weight or of depression by fluids alone.

3 Evidence is presented that small amounts of blocking material stimulate the liberation of antibody, whereas large amounts tends to depress such a liberation.

4 These experiments offer additional evidence that antihodies, at least hemolysin, are formed by the phagocytic cells of the mesenchymal tissues.

The complete report is published in the *Journal of Immunology* (17: 441 [Nov] 1929).

TWO CASES OF MALIGNANT ULCERATIVE ENDOCARDITIS OF THE PULMONARY VALVE W. W. BRANDES, M. D.

The first case is that of a white woman, 25 years of age, whose chief complaint was nausea, vomiting and fever. During the course of the disease, however, joint pain and temperature of the septic type developed, and a murmur was heard over the pulmonic area. After repeated negative results, a positive blood culture was obtained, a nongreen-producing, nonhemolyzing streptococcus growing only on blood mediums and under partial oxygen tension being isolated. Pregnancy had been diagnosed, but criminal abortion was denied. The patient died on the twenty-fourth day in the hospital. The postmortem examination demonstrated massive, irregular, friable vegetations on the pulmonary valves apparently completely occluding the orifice of the pulmonary artery, and similar, but somewhat small, vegetations scattered along the entire length of the posterior wall of the artery to the hilum of the left lung. Numerous emboli were present in the intrapulmonic branches of the pulmonary artery, and multiple hemorrhagic infarcts, but no abscess. Acute fibrinous pleurisy was present. The right side of the heart was markedly dilated. There was a necrotic ulcer at the level of the internal os of the uterus on the posterior wall and a ragged reddish-gray area in the fundic portion. A small amount of thin grayish exudate was present over the rectum and posterior surface of the uterus. The spleen was large and soft. There were numerous petechial hemorrhages and small pustules in the skin of the back.

Histologic preparations contained decidual tissues and chorionic villi in the fundic portion of the uterus.

Gram's stain of the tissues demonstrated gram-positive chain-forming organisms in the vegetations, lungs, spleen, liver, uterus and glomeruli of the kidneys.

The second case was that of a colored man, aged 43, who cut his right thumb on a tin can. The thumb was amputated on the day following the accident, but septicemia developed rapidly and death followed in ten days.

The postmortem examination demonstrated a vegetation 10 by 12 mm on one leaflet of the pulmonary valve and an ulceration of the intima of the aorta with marginal vegetations 5 mm from the valves. There were multiple septic infarcts in the right lung, acute fibrinous pericarditis and pleuritis, a generalized fibrinopurulent peritonitis and descending infection of the kidneys.

These cases were brought before the society because of the infrequency of purely pulmonary valve involvement, but chiefly because of the massive size of the vegetations and special bacteriologic features in the first case.

Book Reviews

DIE BIOLOGIE DER PERSON EIN HANDBUCH DER ALLGEMEINEN UND SPEZIELLEN KONSTITUTIONSLEHRE By T BRUGSCH and F H LEWY Numbers 9 to 14 Berlin Urban & Schwarzenberg, 1929

The recent issues of this work contain several contributions of special interest to the pathologist. M. de Crim devotes an extensive article to the question of the humoral constitution. His discussion is based on the conception that for the organs of the human body, and in particular for the central nervous system, the body fluids belong to the outer world as do the fluid mediums in which the low forms of animal life exist. Arnold Josefson's chapter on the personality and the endocrine glands does not cover the field as completely as it would seem desirable. The personality is intimately influenced by the inner secretory glands. There exists an undetermined optimum in the activity and internal relation of the endocrine glands which secures the greatest efficiency in the defense against internal and external injuries. It is the inner secretory system which, to a great extent, determines the personality, and disturbances in this system are of great significance especially during the years of development.

In the period of cellular pathology the supporting structures were greatly neglected. The modern conception of constitution has given to these structures a paramount importance, since it is through them that the habitus of the individual is fixed. K. H. Bauer succeeds well in illustrating the part played by the connecting substances in the different problems of constitutional pathology.

Much valuable information also can be obtained from R. Weber's study on the teeth. Then follow two detailed chapters on the intestinal tract by F. Fleischer and on the eye by J. Helbron. The reviewer can recommend especially the latter chapter, which contains much valuable material for both the pathologist and the pharmacologist. Much space is devoted to the question of the influence of the environment (R. Michels) and the climate (F. Giese) on the person.

It is, of course, difficult to define sharply what should be included in a system of the biology of the person. There are chapters of a philosophic and religious content, dealing with the person and the community in their relation to Catholicism (L. Bopp), evangelical Christianity (C. Fabricius), Islam (H. H. Schaefer) and Judaism (S. B. Rabinow). A. S. Steinberg discusses the person in old and new Russia, Sen Nagai in Japan and Betty Heimann in the Indian view of the world. Sen Nagai also describes the constitution of the Japanese. The remaining contributions are: H. Schulte, the psychology of the sport and constitution; R. Allers, medical characterology; and K. Birnbaum, the problem of biophysics in constitution.

THE MEDICAL MUSEUM, MODERN DEVELOPMENT, ORGANIZATION AND TECHNICAL METHODS BASED ON A NEW SYSTEM OF VISUAL TEACHING By S. H. DAUKES, OBE, MD, DPH, DTM and H., Director of the Wellcome Museum of Medical Sciences. Pp. 172, with 44 illustrations. London: The Wellcome Foundation, Ltd., 1929.

This volume is an interesting and important contribution to medical museology. A comprehensive system of linking various departments in medicine in synoptical demonstrations of great educational value is described in detail. The time has come when the medical museum must expand from being merely a collection of pathologic specimens into a living, progressive representation of medical knowledge and methods. This is the plan followed by the Wellcome Museum of Medical Science in London, and practically all of the forty-four full page illustrations in the book illustrate the exhibits and methods of that museum. The first chapter deals with the need of expanding the medical museum so that it may represent the growth of medicine as a whole, and the functions of the museum in this wider outlook in collecting and preserving material, in research and in education are set forth clearly and enthusiastically. By education in this connection is meant not only specific medical education but also the education of the public.

in matters of health and hygiene. In chapter 2 the evolution of the system of the Wellcome Museum is outlined. Chapter 3 is concerned with the general arrangement, classification, sequence and grouping of specimens and exhibits. The succeeding five chapters deal with exhibits illustrating individual diseases under etiology, pathologic anatomy, symptomatology, treatment and prevention. These chapters will be of much service to persons in charge of growing museums of larger scope than just preserving and exhibiting pathologic specimens. Curators of such collections, however, will find much of interest and help in these chapters, particularly in chapter 5, which discusses the grouping collection, preparation, etc., of pathologic material. In chapter 9 the possible objections to the synoptical method of demonstration are analyzed and answered. The last chapter discusses the museum of the future. "A museum lives more by what it gives than by what it receives"—in other words, the museum should not be treated merely as a depository of material but as an integrating and living influence in teaching medical knowledge. In several appendices various problems of museum arrangement and methods are discussed with particular reference to carrying out the synoptical scheme. Finally come lists of references to museum methods. The book will be a helpful and stimulating guide to all who are concerned in developing progressive medical museums.

TULAREMIA. HISTORY, PATHOLOGY, DIAGNOSIS AND TREATMENT. By WALTER M. SIMPSON, M.D., Director of Diagnostic Laboratories, Miami Valley Hospital, Dayton, Ohio. Price, \$5.00. Pp. 162, with 53 illustrations and 2 color plates. New York: Paul B. Hoeber, Inc., 1929.

The growth of knowledge of tularemia is one of the most romantic chapters in the recent history of medical research. The first case in a human being was recognized by Wherry in 1912. In 1920 the term "tularemia" could not be found in the medical literature, and up until 1924 only 15 cases had been reported. During the next four years (1924-1928) over 800 cases were recognized in the United States, a large number of which were studied in the Hygienic Laboratory of the U. S. Public Health Service. The work of George W. McCoy, who discovered the organism of tularemia, and of Edward Francis, both of the U. S. Public Health Service, constitutes the foundation of our knowledge in this "new disease." In 1925 it was recognized by O'Hara in Japan, and in 1928 by Russian workers in the province of Astrakhan. Dr. Simpson has written an interesting and timely book on this disease. Here under one cover is a complete and accurate account of the history, distribution, clinical manifestations, pathology, bacteriology, diagnosis and treatment of tularemia. The author has emphasized certain features, namely, (1) the certainty of infection of laboratory workers, (2) the persistence of agglutinins in the blood of long-recovered patients, (3) the cross agglutination of *Bacterium abortus* and *Bacterium tularense*, (4) the granulomatous character of the lesions in man as contrasted with the lesions in animals, (5) the cystine requirements of the organism in culture mediums, (6) its pleomorphism, (7) its penetration of the unbroken skin, (8) its invasion of fixed tissue cells, (9) its transmission through the egg of the tick to the next generation of ticks, (10) the great variety of insect hosts, (11) the great variety of animal hosts. There is a complete bibliography.

THE BLOOD PICTURE AND ITS CLINICAL SIGNIFICANCE (INCLUDING TROPICAL DISEASES). A GUIDEBOOK ON THE MICROSCOPY OF THE BLOOD. By PROFESSOR DR. VICTOR SCHIFF, Physician-in-Chief, the First Medical University Clinic, Charité, Berlin. Translated and edited by R. B. H. GRADWOHL, Director of the Pasteur Institute of St. Louis, and the Gradwohl School of Laboratory Technique. Seventh and eighth revised edition. Price, \$10.00. Pp. 408, with 44 illustrations and 4 color plates. St. Louis: C. V. Mosby Company, 1929.

The first edition of this book was published in 1912. To this edition have been added sections on the typing of blood, the "guttadiaphot method," a discussion of Arneith's "Qualitative Blood Theory," the *Bastone* group of *Verruca peruviana*.

The discussion of sedimentation of red corpuscles has been enlarged. Part 1 deals with technical matters. Here one notes that some of the methods would be difficult to carry out in the United States because the stain required or the particular instrument is not readily available. It is a disadvantage, too, that the chart for differential leukocyte count, on page 55, is reproduced with German designations. "Guttadiaphot" means a drop of blood viewed by transmitted light, the test appears to need special paper available in Germany. Part 2 deals with theory, morphology and division of the blood picture, and Part 3 with the fundamental principles for clinical use of the blood picture. The blood picture includes the erythrocyte picture as seen in smear and thick drop, the differential leukocyte picture in smear, the total number of leukocytes as determined by estimation or count, the number of red cells and the color index. Part 4 gives selected examples of the practical use of blood pictures or hemograms. There is a disease index with brief blood pictures, as well as a general index. The bibliography gives references chiefly to the German literature and there are no references to literature in the English language. There seems to be no reference in the book to sickle-cell anemia. The translator, who has done his work faithfully, expresses his belief that Schilling's book represents a marked advance in morphologic hematology and that it will be of great advantage to learn his methods.

THE DEVELOPMENT AND GROWTH OF THE EXTERNAL DIMENSIONS OF THE HUMAN BODY IN THE FETAL PERIOD. By RICHARD E. SCAMMON, Professor of Anatomy in the University of Minnesota, and LEROY A. CALKIN, Professor of Gynecology and Obstetrics in the University of Kansas. Price, \$10.00. Pp. 367. Minneapolis: The University of Minnesota Press, 1929.

This is a monographic presentation of a noteworthy, quantitative study of fetal growth. "It consists of an account of the changes in the dimensions and external proportions of the body as determined from a large number of original observations and from a colligation of all available published data by other investigators. These data have been treated analytically, studied for the effects of various important artifacts on them, and are presented, in condensed tabular, graphic and analytic forms." The original data were obtained by about 35,000 measurements of 71 external dimensions of upward of 400 selected human fetuses ranging from 23 to 544 cm in crown-heel length. Measurements were made also on 33 living newborn infants, but the data on these are not included in the final tabulations. Following a detailed statement of the general plan of the investigation are given the summaries of the measurements, a general discussion and a general summary. There is an extended bibliography, 180 tables, 73 figures, and 70 field graphs. In the preface by Prof. C. M. Jackson it is pointed out that the main outcome of this impressive work is a new principle, namely, that "in general the linear growth of the various parts of the body is in uniform ratio during the fetal period." Any changes in proportion during this period appear to arise from irregularities established in the earlier, embryonic period. The work of the publisher is appropriate and commendable. This monograph will be an essential source of reference to students of the problems of growth.

THE ADRENALS, THEIR PHYSIOLOGY, PATHOLOGY AND DISEASES. By MAX A. GOLDZIEHER, Former Professor of Pathology, University of Budapest, Director of Laboratories, United Israel Zion Hospital, Brooklyn. Pp. 436, with 73 text-figures. New York: The Macmillan Company, 1929.

The purpose of this book is to summarize the present knowledge concerning the suprarenals, their structure, physiology and diseases. It represents apparently an expansion of an earlier monograph by the author which was based on his own experimental and anatomic studies. There are six chapters, which deal with the following subjects: development, anatomy, physiology, pathologic anatomy, pathologic physiology and suprarenal organotherapy. The longest chapters are the two dealing with pathologic anatomy and physiology of the suprarenals. There are

seventy-three text-figures most of them illustrating the microscopic appearances of morbid changes in the suprarenals. Unfortunately for some reason many of the figures are so indistinct as to be worthless. There is an extensive bibliography, covering more than 100 pages. The references are given under topics in alphabetical order according to authors' names. The various topics are not located easily without first consulting the index in which the bibliography is referred to by pages under the main subjects. The use of special abbreviations of the names of periodicals, requiring a key, seems to be an unnecessary complication that could have been avoided by following the standard style of abbreviations of the *Quarterly Cumulative Index Medicus*. The style is not consistently clear and direct. The book contains a large amount of information about the suprarenals and their many and difficult problems. It will be of value as a base for sources to the student of the suprarenal gland.

SELECTED READINGS IN PATHOLOGY FROM HIPPOCRATES TO VIRCHOW. Edited by ESMOND R. LONG, Professor of Pathology in the University of Chicago. Price \$4. Pp. 301. Springfield Ill. Charles C. Thomas, 1929.

The volume contains a set of excerpts (English) from medical classics of particular significance to the study of pathology as commonly understood. Some of these excerpts mark milestones in the development of knowledge of disease, while others are samples of writings that have had exceptional influence. The time covered extends to the publication in 1863 of the translation by Frank Chance of Virchow's *Cellularpathologie*, that is roughly to the beginning of the microbic era. It is the gradual replacement of "humoral" by "cellular" pathology that is illustrated by the book, infection and immunity do not come within its scope. Thirty-six masters are represented, and of these, three are American—Horner, Gerhard, Gross. The order in which the excerpts come is chronologic. Each excerpt is preceded by a brief but illuminating characterization of the work of the author by the editor. There are twenty-five illustrations, mostly of authors themselves. The work of the publisher merits a word of commendation. There is now available in attractive form a well selected and representative set of documents, all in English and of convenient length, illustrating the development of pathology. Many of the works from which excerpts are taken are often quoted especially in the courses on pathology, but for various reasons only seldom, very seldom read. Long's Readings makes it easy to form a more intimate acquaintance with these classic writings and supplements well his excellent *History of Pathology*.

BLOOD GROUPING IN RELATION TO CLINICAL AND LEGAL MEDICINE. By LAURENCE H. SNYDER D.Sc., Associate Professor of Zoology, North Carolina State College, Raleigh, Committee on Blood Grouping, National Research Council. Price, \$5.00. Pp. 153, with 28 illustrations and 5 plates. Baltimore: Williams & Wilkins Company, 1929.

Snyder's book is the first comprehensive American book on the theory and practice of blood grouping. The author is in the field of his special competence, as he is an active worker on grouping problems particularly as they touch genetics and physiology. Fortunately he is experienced also in practical transfusion, which is discussed in considerable detail. The book may be divided as follows: the principles of isohemagglutination, transfusion—history, indications, technic of blood testing, methods, blood groups in legal medicine and in pathology, blood groups in animals, racial distribution of blood groups and its anthropologic significance. In other words, the trends of interest in and the practical applications of, blood grouping are considered. There is an extensive bibliography. The materials are handled adequately and the style is clear and direct. The book will be useful for all who are interested in blood grouping.

Books Received

REPORT OF THE HAFFKINE INSTITUTE FOR THE YEAR 1928 By Major S S Sokhey, I M S Officiating Director, Haffkine Institute Price, 2 annas or 3 pence Pp 43 Bombay Government Central Press, 1929

INFECTIOUS DISEASES AND OTHER FEVERS IN INDIA A MANUAL FOR STUDENTS AND PRACTITIONERS By Purshotamdas T Patel, M D (London), M R C P (London), D T M & H (Cantab), F C P S (Bombay), Medical Superintendent, City Isolation Hospitals (Arthur Road) and Maratha Plague Hospital, Hon Physician, King Edward VII Memorial Hospital and Turner Sanatorium for Tuberculosis Clinical Professor of Infectious Diseases, Medical Colleges, Bombay Calcutta and London Butterworth & Company, Ltd, 1929

A SURVEY OF THE LAW CONCERNING DEAD HUMAN BODIES By George H Wennmann Bulletin 73 of the National Research Council Issued under the Auspices of the Committee on Medicolegal Problems, National Research Council Price, \$2 Pp 199 Washington, D C National Research Council, 1929

EPIDEMIC ENCEPHALITIS ETIOLOGY, EPIDEMIOLOGY, TREATMENT Report of a Survey by the Matheson Commission William Darrach chairman, Haven Emerson Frederick P Gay, William H Park, Charles R Stockard, Frederick Tilney, Willis D Wood, Hubert S Howe, secretary, Josephine B Neal, director of survey, and Helen Harrington, epidemiologist Price \$3 Pp 849, including bibliography and author and subject indexes New York Columbia University Press, 1929

THE IMMUNOLOGY OF PARASITIC INFECTIONS By William H Taliaferro, Ph D Professor of Parasitology, the University of Chicago Price, \$6 Pp 414 New York Century Company, 1929

MEDICAL LEADERS FROM HIPPOCRATES TO OSLER By Samuel W Lambert, M D, and George M Goodwin, M C Price, \$5 Pp 331, with 32 illustrations Indianapolis Bobbs-Merrill Company, 1929

THE RIGHT HONOURABLE SIR THOMAS CLIFFORD ALLBUTT, K C B, M A M D, F R C P, F R S, Hon M D, D Sc, D C L, LL D, Regius Professor of Physic in the University of Cambridge, Fellow and Sometime Classical Scholar of Gonville and Caius College A Memoir By Sir Humphry Davy Rolleston, Bart, G C V O, K C B, M A M D, Hon M D D Sc D C L LL D, Regius Professor of Physic in the University of Cambridge, Sometime President of the Royal College of Physicians of London Price, \$6 Pp 314 New York The Macmillan Company, 1929

DISEASES TRANSMITTED FROM ANIMALS TO MAN By Thomas G Hull Chief Bacteriologist, Illinois Department of Public Health, Assistant Professor of Pathology and Bacteriology, University of Illinois, College of Medicine With an Introduction by Veranus A Moore, Director, New York State Veterinary College, Cornell University Price, \$5 50 Pp 352, with 29 illustrations 43 tables and index Springfield, Ill Charles C Thomas, 1930

A NEW METHOD FOR DIFFERENTIAL STAINING OF PLASMA CELLS AND OF OTHER BASOPHILIC CELLS^{*}

CHARLES H. HITCHCOCK, M.D.

AND

WILHELM EHRLICH, M.D.†

NEW YORK

The methyl-green pyronin mixture of Pappenheim and Unna, while serving a useful purpose in the staining of basophilic cytoplasmic substance in numerous varieties of cell, suffers a certain diminution of value, in that for the securing of best results preliminary fixation of the tissue in absolute alcohol is requisite. Material fixed in Müller's solution plus formaldehyde can usually be satisfactorily stained after subjecting the slides to a preliminary soaking in alcohol, but the use of other reagents is as a rule followed by failure. The more frequent use in this laboratory of Zenker-acetic acid solution for routine fixation has led to a search for another formula by the use of which there might be secured comparable differential staining of material so treated. Stropeni¹ stated that the substitution of acridine red for pyronin accomplishes this result, and presented two formulae for preparing the staining mixture. Attempts in this laboratory to utilize his methods have been unsuccessful, in that uniform overstaining by the red dye has constantly occurred. Efforts to overcome this defect by reducing the relative amount of the acridine red or by lengthening the period of differentiation have resulted merely in complete failure of differential staining. In view of the fact that even in successful Unna-Pappenheim preparations, the nuclear staining is rather weak, it was felt that the substitution of another nuclear dye for the methyl green might be of advantage. Malachite green was tested and was found to answer the purpose admirably.

The staining fluid finally adopted consists of a mixture of a 2 per cent aqueous solution of malachite green with a 2 per cent aqueous solution of acridine red, in the proportion of one part of the former to three of the latter. This mixture keeps well and does not show any

^{*} Submitted for publication, Sept. 6, 1929.

[†] From the Hospital of the Rockefeller Institute for Medical Research.

[†] With the technical assistance of Jessie C. Hon.

¹ Stropeni, L. Una nuova miscela per la colorazione delle plasmazellen. *Ztschr. wissenschaft. Mikr.* **39**: 302, 1912.

precipitation. A few weeks' ripening of the mixed solutions is of advantage, though excellent results are secured when the stain is employed as soon as prepared. Only Grübler's dyes have been used. Sections prepared by the paraffin method are passed through iodine in the usual manner. The iodine is removed by graded alcohols followed by thorough washing in running water for at least fifteen minutes, incomplete removal often results in precipitation of the stain. The slide is then flooded with the dye solution for from fifteen to thirty seconds.

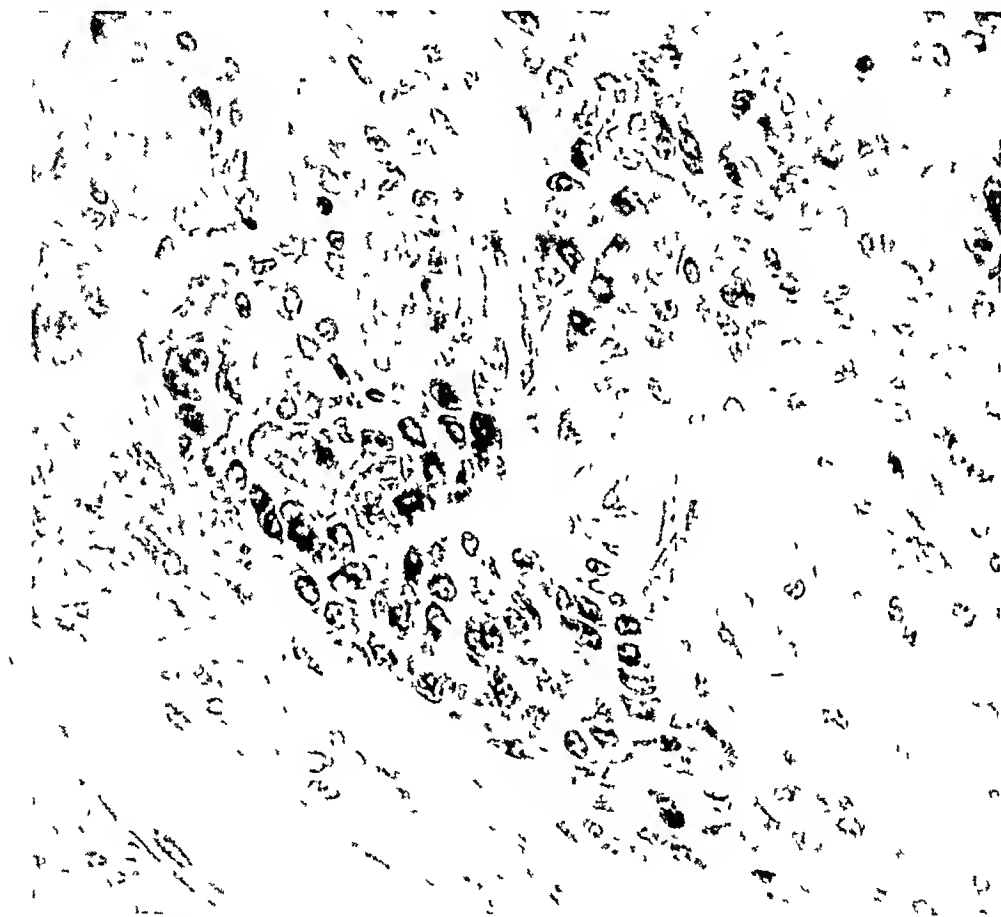


Fig 3—Another portion of the same tonsil as in figure 1, showing perivascular infiltrate containing basophilic cells and particularly rich in plasma cells, $\times 560$

The excess of solution is drained away, and the slide is rapidly washed in water. It is then passed directly into absolute alcohol, where it is left only as long as the dye continues to be washed out in clouds. It is then transferred quickly into xylene. Occasionally, the brilliancy of the preparation is enhanced by restaining.

Comparative observations have shown that alcohol-fixed material is well stained by this method, but such sections are more deeply colored by the Unna-Pappenheim formula. On the other hand, tissue fixed in corrosive sublimate or in Zenker-acetic acid solution yields better prepa-

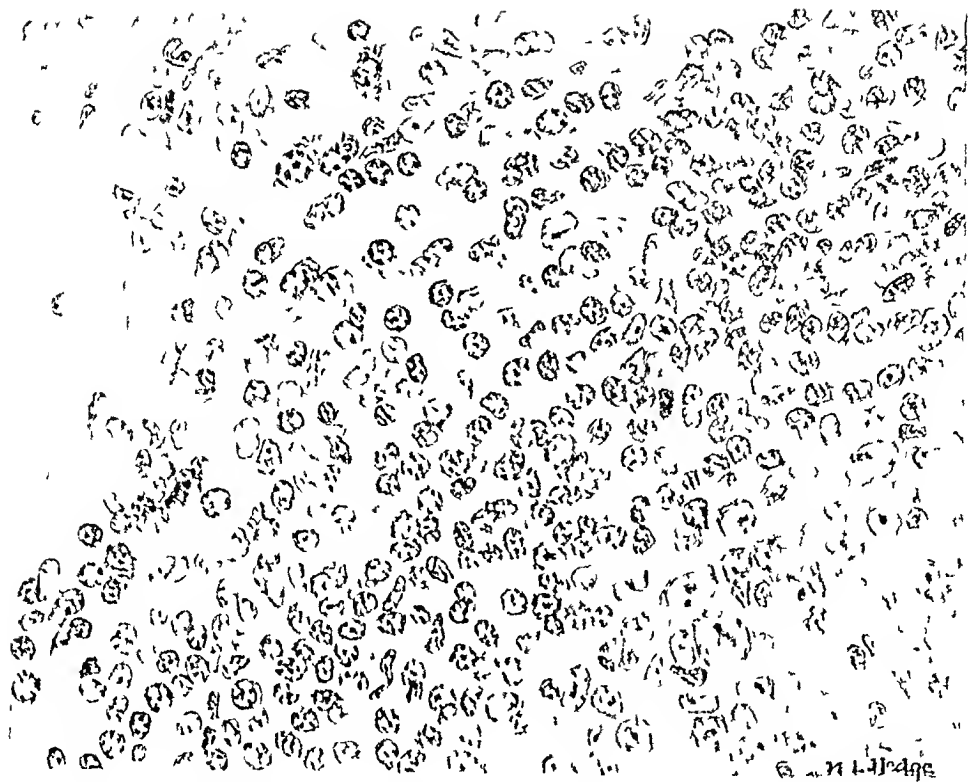


Fig 1—Section of tonsil from patient with rheumatic fever Plasma cells in margin of lymphatic tissue "Germinal center" in lower right hand corner All sections are stained by the malachite-green acridine-red method This section is here magnified 750 times

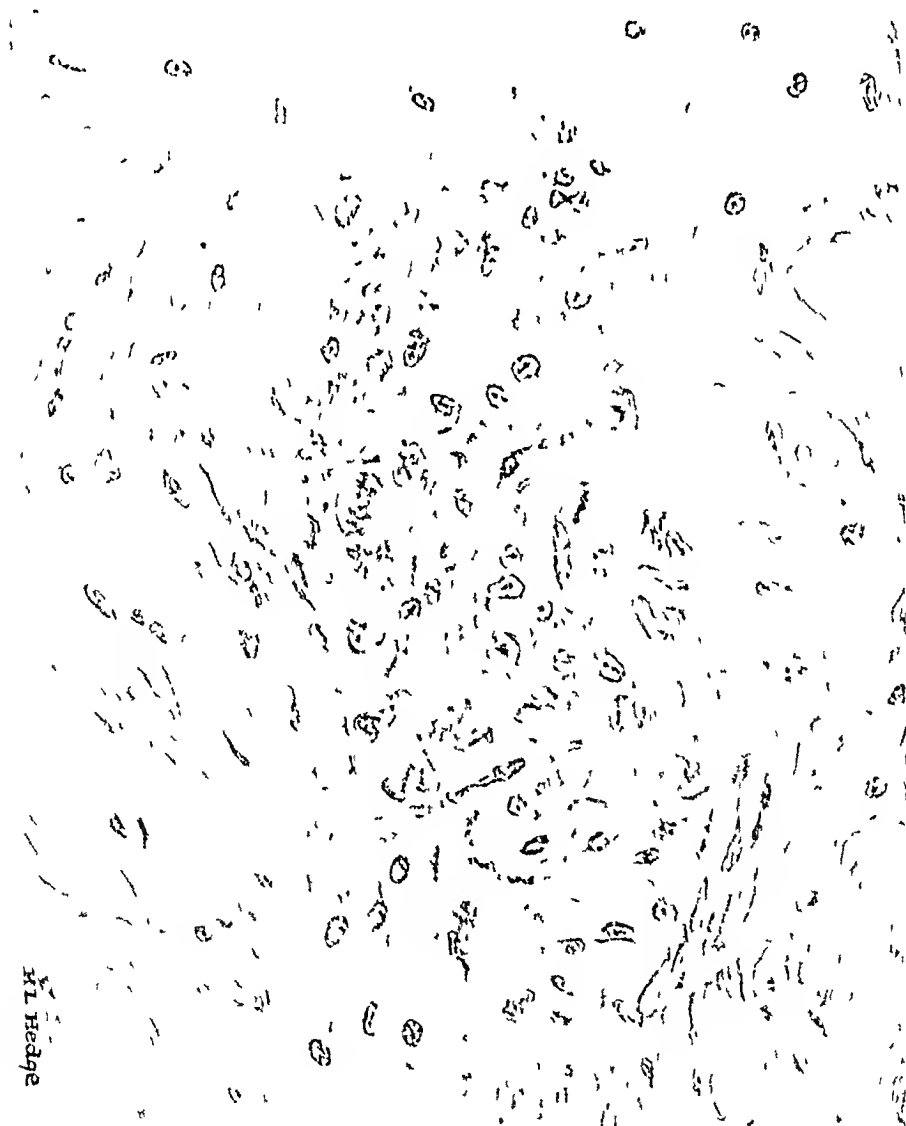


Fig 2—Aschoff body in heart muscle of patient dying with rheumatic fever, $\times 450$

rations when the malachite-green acridine-red mixture is employed. Results in fixation with Muller's solution plus formaldehyde have been unsatisfactory, even when the slides have been subjected to preliminary overnight soaking in alcohol.

This method presents certain advantages in addition to its applicability following Zenker-acetic acid fixation. The brilliancy and depth of color of a successful pyronin stain tend to obscure detail, and in addition there is usually a certain degree of pink color throughout the section.

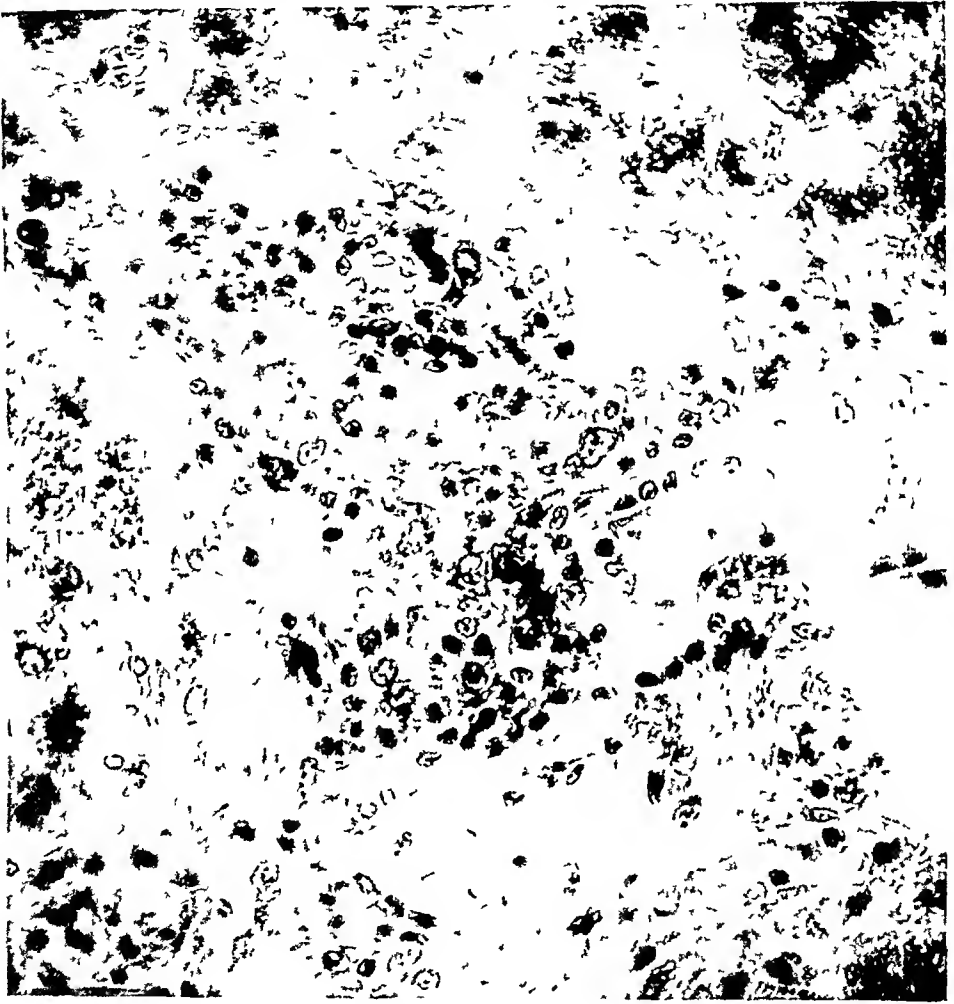


Fig 4—Experimentally produced perivascular exudate in rabbit's liver, $\times 560$

Acridine red, while not yielding the same depth of color, does not cloud the picture, even when minute detail is studied with the oil-immersion objective. There is no confusing background of pink, so that the differential staining of the basophilic substance, while more delicate and of a lighter hue, is just as distinctive as in the case of more deeply colored preparations. Furthermore, the superiority of malachite green over methyl green as a nuclear stain is highly advantageous. While

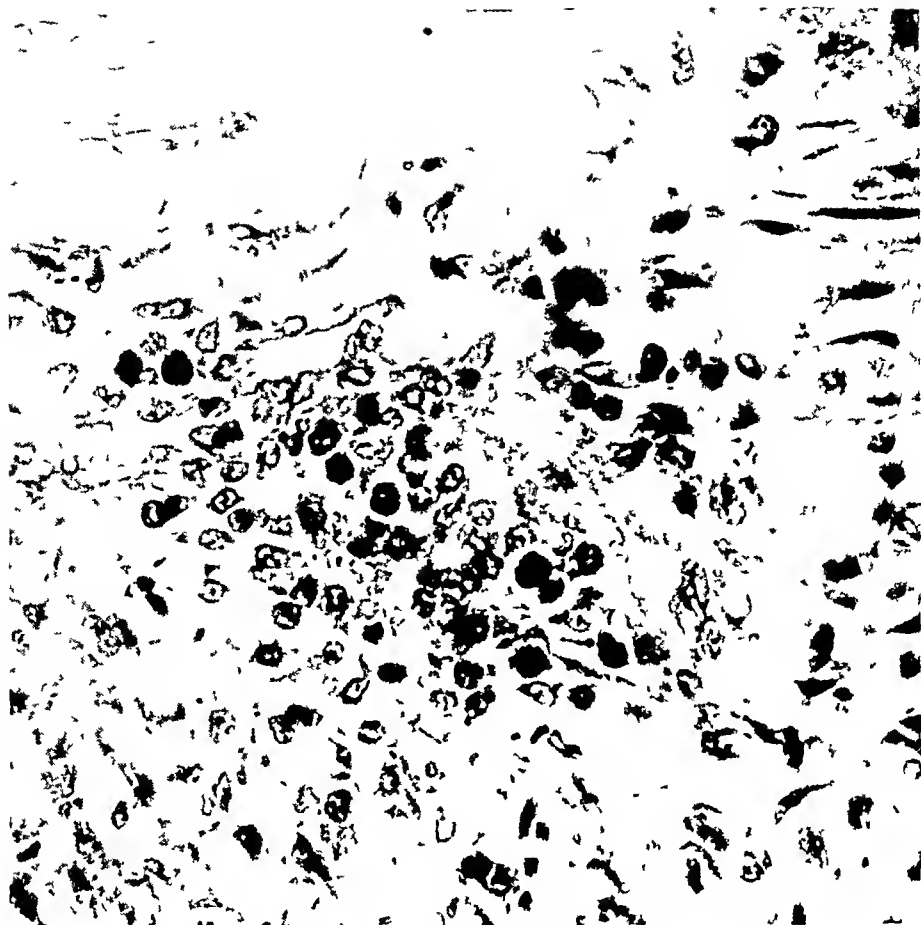


Fig 5—Infiltration around infected agar focus in subcutaneous tissue of hyperergic rabbit, $\times 560$

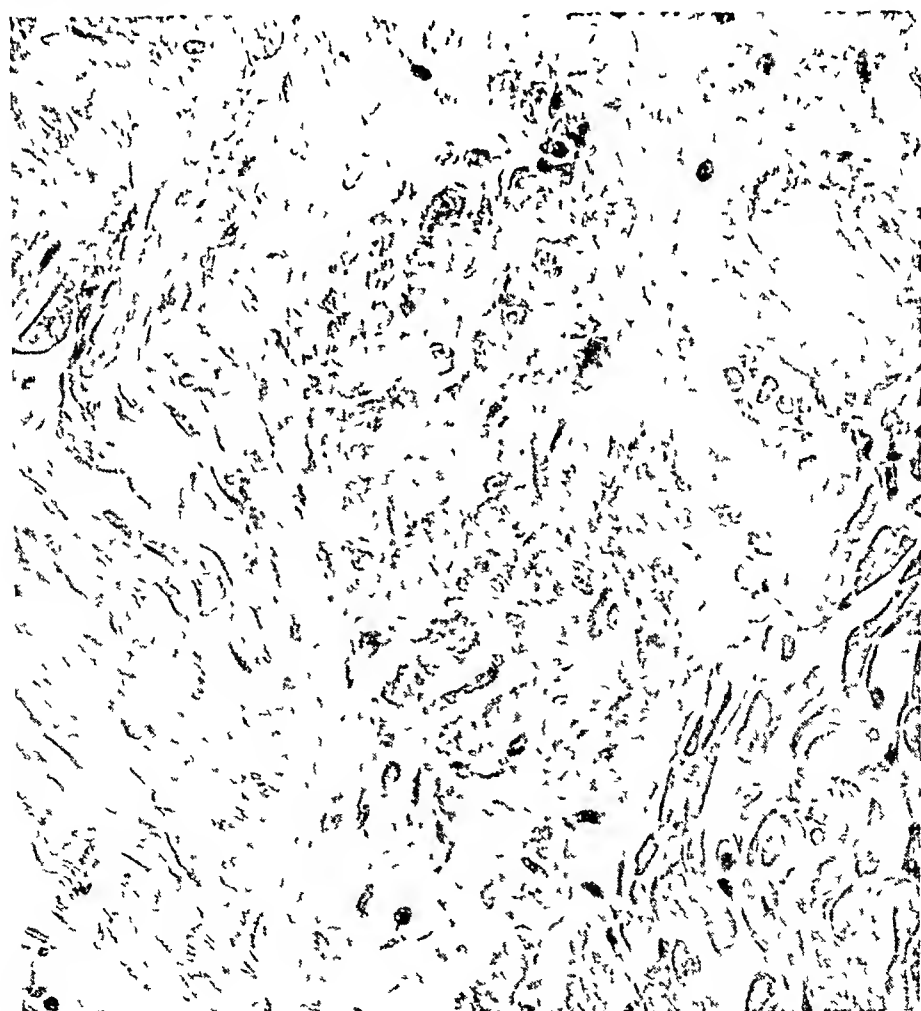


Fig 6—Same Aschoff body as in figure 2, $\times 470$

not so detailed as that secured by the use of iron hematoxylin or of safranin, the delineation of the nuclear structure is sharp and clear, and provides an excellent contrast with the various shades of cytoplasmic red. Certain other structures are stained by this nuclear dye, as, for instance, striated muscle, fibrin and certain pigments.

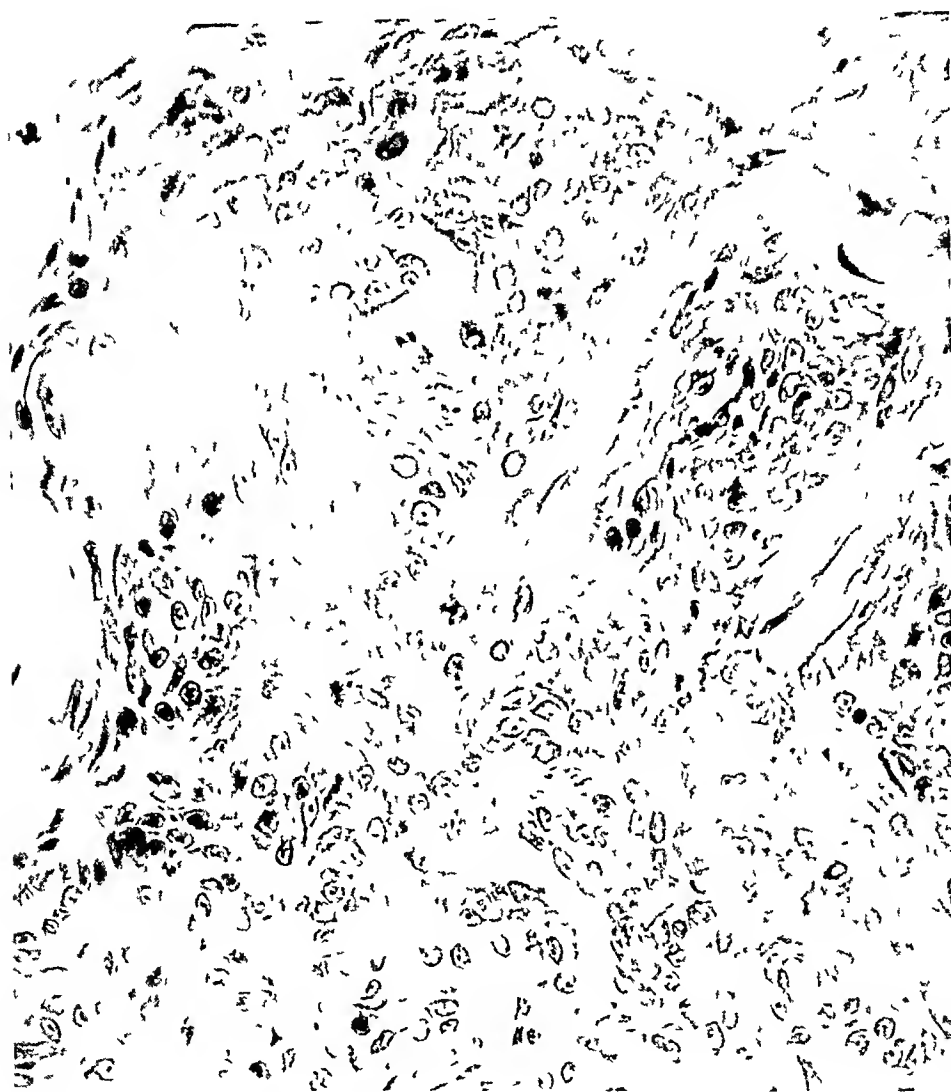


Fig 7—Subcutaneous nodule removed at biopsy from patient with rheumatic fever. Various degrees of tissue basophilia are present. $\times 470$

Results par excellence are secured when lymphatic tissue is prepared by this method. In the colored figure 1, which is derived from a specimen of tonsil, the deep hue of the plasma cells contrasting with the lighter and brighter tint of the large cells of the so-called germinal center, is well seen. Nuclear detail is clear and sharp. In the photomicrographs, it is of course difficult to portray the differential staining to the same degree, but comparison of figure 3 with figure 1, both from

the same slide, will aid in the interpretation of the former. Other basophilic cytoplasm, such as that of many young or functionally active cells, is colored in various shades of red or pink. Ganglion cells are deeply stained, so also are many of the immature cells of bone-marrow. In figure 4 is pictured an experimentally produced perivascular infiltration within which basophilic cells are present and can easily be identified. Figure 5 represents a hyperergic tissue reaction in which many deeply basophilic cells are present.

The cytoplasm of the characteristic cells of the Aschoff body is stained a rather dull, smudgy red, which varies considerably in depth from cell to cell, and is distinct in quality from the brighter hues seen in young or functionally active cells (compare figs 1 and 2). This peculiar tone-quality was noted by Aschoff² and by him was ascribed to degeneration of the cell. In young subcutaneous rheumatic nodules may be found great numbers of basophilic cells, some with brilliantly staining protoplasm, others characterized by the dull dirty red of the Aschoff's body cell. Similarly staining cells are frequently encountered in other rheumatic tissues. The peculiar dulness of color noted in many of the cells of rheumatic tissue is rather distinctive, and it seems possible that systematic investigation with this method may shed further light on the disputed questions of their origin and nature. Figures 6 and 7 and the colored figure 2 reveal more fully than any description the exactness of detail secured by this method, and its applicability to study by high magnification.

SUMMARY

By the use of malachite green and acridine red, the Unna-Pappenheim staining method has been so modified as to be applicable to tissue fixed in Zenker-acetic acid solution. Such preparations are better adapted to study by high magnification. This modification is particularly valuable in the study of lymphatic tissue and of rheumatic fever material.

² Aschoff, L. Zur Myocarditisfrage, Verhandl. d. deutsch. path. Gesellsch. 8: 46, 1904.

OXYURIS VERMICULARIS IN THE PERITONEUM *

RAYMOND H. GOODALE, M.D.

AND

HARALD KRISCHNER, M.D.

BEIRUT, SYRIA

Infection of the peritoneum with *Oxyuris vermicularis* is not a common disease, and the following case illustrates the difficulty of diagnosis at operation. The surgeon made a diagnosis of tuberculous peritonitis at laparotomy and sent a nodule to the department of pathology for histologic section. The tissue proved to be *Oxyuris vermicularis* walled off in the peritoneum.

REPORT OF CASE

A married woman, aged 21, entered the hospital on April 25, 1928, complaining of the continuous passing of urine through the vagina, beginning with her last delivery six months before. The only other complaint was amenorrhea, which also began at that time.

The physical examination showed nothing abnormal, except that there were only vestiges of the urethra left. A fistula admitting one finger opened from the vagina into the base of the bladder. This fistula was surrounded by dense scar tissue. Beyond the fistula, the vagina appeared as a narrow transverse slit between rigid cicatricial lips. The patient was advised to have a transplantation of the ureters into the colon.

In the course of ureterocolostomy, several loops of small intestine were found covered with hard white nodules, each slightly smaller than a pea. These nodules were diagnosed as tubercles. One was excised, fixed in Kaiserling I solution, dehydrated, embedded in paraffin and stained with hematoxylin and eosin and Gram's stain. On microscopic examination, the tissue showed two cross sections of a female oxyurid filled with eggs (fig. 1). The wall of the parasite was clearly outlined, and the two lateral spurs helped to identify it. Immediately surrounding the worm was a zone of degenerating tissue, in which no definite cellular structure could be made out. The outer zone was made up of concentrically arranged connective tissue cells, among which were eosinophils and histiocytes. No giant cells were found around the parasite and no bacteria were found by the Gram method.

A few cases of *Oxyuris* encapsulated in the peritoneum similar to the one described now are reported in the literature. At the autopsy of a 42 year old woman who died of carcinoma of the breast, Kolb¹ found ten hard nodules on the peritoneum of the pelvis. These nodules were white, the size of grains of rice, and some of them were pedunculated. With the exception of one *Ascaris lumbricoides* in the esophagus, there were no parasites of any kind in the gastro-intestinal tract. The

* Submitted for publication, Nov. 7, 1929.

From the Department of Pathology, American University of Beirut.

¹ Kolb. Centralbl. f. Bakteriologie (Orig.) 31: 268, 1902.

mucosa of the rectum was normal, and the vagina, uterus and tubes showed no changes. Microscopic examination of the nodules showed numerous ova of *Oxyuris vermicularis*. Schneider's² case was similar. At the autopsy of a 36 year old woman who died of diffuse peritonitis after a hysterectomy, he found a nodule 2 cm in diameter near the operative stump of the left ovarian ligament, which showed a mature oxyurid surrounded by connective tissue and containing ova. Marro³ reported a case of an oxyurid found at autopsy in a 34 year old woman



Section of *Oxyuris vermicularis* showing ova

from an insane asylum. Two small growths were situated on the outside of the left tube near the fimbriated end, one the size of a pea and the other twice as large. In situ, they were thought to be the remains of an old peritonitis. Both were cystic, containing clear cholesterol crystals in fluid. The smaller one contained numerous ova of *Oxyuris*. Histologic examination of the cyst excluded the possibility of a direct extension through the wall of the tube. Strada⁴ also found an encap-

2 Schneider Centralbl f Bakteriol **36** 550 1905

3 Marro, G Arch per le sc med **25** 161 1901

4 Strada, F Arch per le sc med **31** 418, 1907

encapsulated oxyurid on the peritoneal surface of the pouch of Douglas in a 60 year old woman who had died of bronchopneumonia. Schroeder⁵ reported a similar case. Kaufmann⁶ found *Oxyuris* in tissue from a 31 year old woman removed during laparotomy.

The chief question concerning these cases of encapsulated *Oxyuris* on the peritoneum has to do with the mode of entrance into the peritoneal cavity. There are two possibilities: one is by way of the genitalia in females and the other is by direct extension through the wall of the intestine. It is agreed by most writers that the oxyurid gains access to the peritoneal cavity in females by way of the vagina, uterus and tubes. This seems logical because oxyurids have been found in all of these at different times. Heller⁷ found oxyurids incidentally in the vagina at autopsy, while Spitzer⁸ found many living worms (oxyurids) in the solution following a vaginal douche in a 12 year old girl. Westphalen⁹ mentioned having seen these parasites near the cervix. Simons¹⁰ found them living and motile in the cervix of a living woman, and Vix¹¹ reported that he found the eggs in uterine secretions.

The only instance in which the uterus was found to be infected was the case of Benedetti¹² in which he found *Oxyuris* between the placenta and the uterine wall.

Chiari¹³ found the female parasite surrounded by giant cells in a tube with salpingitis of long standing. He assumed that the parasite gained entrance to the tube by way of the vagina and cervix, because *Oxyuris* had been found in these locations. Tschamer¹⁴ found two living oxyurids in the right tube of a 31 year old woman.

It will be noted that all the cases of encapsulated oxyurids in the peritoneum were in women. Entrance to the peritoneal cavity by way of the genitalia seems reasonable. However, there are certain cases in which abscesses caused by *Oxyuris* have been found in the intestinal wall, and these cannot be explained in the same way. Nathan¹⁵ reported a case in a young workman with a perirectal abscess in which

5 Schroeder. Lehrbuch der Gynakologie, ed 2, Leipzig, F. C. W. Vogel, 1926.

6 Kaufmann. Lehrbuch der speziellen pathologischen Anatomie. Berlin, W. de Gruyter & Company, 1922, p. 672.

7 Heller. Deutsches Arch. f. klin. Med. **77**: 21, 1903.

8 Spitzer. Wien. med. Wchnschr. **42**: 6, 1892.

9 Westphalen, cited by Kolb (footnote 1).

10 Simons. Zentralbl. f. Gynak. **23**: 777, 1899.

11 Vix, cited by Kolb (footnote 1).

12 Benedetti, cited by Kolb (footnote 1).

13 Chiari, H. Virchows Arch. f. path. Anat. **269**: 730, 1928.

14 Tschamer. Zentralbl. f. Gynak. **43**: 989, 1919.

15 Nathan. Frankfurt Ztschr. f. Path. **36**: 82, 1928.

he found the eggs of *Oxyuris* but no bacteria Weigmann¹⁶ and Froelich¹⁷ cited similar perirectal abscesses in two boys 6 and 11 years old, respectively Dmitrieff¹⁸ reported a case of intestinal obstruction as a result of a partly perforated abscess due to *Oxyuris* in the colon The appendix was normal but filled with oxyurids Hippus and Lewinson¹⁹ found *Oxyuris* under the serosa of the appendix of a 6 year old girl They also found eggs of *Oxyuris* in contiguous lymph glands There were no bacteria in the wall of the appendix in this case The parasites must have traversed the intestinal wall in these cases If they went through an opening in the wall passively, all the abscesses should contain bacteria, as well as the oxyurids With the present data however, it seems impossible to draw any definite conclusion

The pathologic effects of encapsulated oxyurids in the peritoneum are not grave, according to Strada who drew this conclusion from the cases which he found described in the literature and from his own case The same is true of the case here reported, for the patient has had no further symptoms referable to the remaining nodules in the peritoneum It appears that the parasites entered the peritoneal cavity bringing with them few if any bacteria from the genital tract The peritoneum reacted against the worms as it would react against any foreign body, by encapsulation

SUMMARY

A case of *Oxyuris vermicularis* encapsulated in the peritoneum is reported, and a review of reports of similar cases is given All the seven cases reported have been in women Since oxyurids have been found in various parts of the genital tract it is concluded that they gain access to the peritoneal cavity by this route No serious pathologic effects have been noted from the encapsulation of *Oxyuris* in any of these cases The cases of abscesses in the intestinal wall caused by *Oxyuris* are also discussed

16 Weigmann Berl klin Wchnschr **58** 732, 1921

17 Froelich Rev mens d mal de l'enf **15** 497, 1897

18 Dmitrieff Zentralbl f Chir **53** 1876, 1926

19 Hippus and Lewinson Deutsche med Wchnschr **43** 1781, 1907

TRAUMATIC RUPTURE OF THE HEART

REPORT OF A CASE *

HENRY W FERRIS, M D

NEW HAVEN, CONN

Spontaneous rupture of the heart associated with some definite existing lesion in the myocardium, such as an infarct has been frequently observed and reported, likewise, wounds and rupture due to perforation by fractured ribs, bullets and various other types of foreign bodies. On the other hand, rupture due to a more indirect trauma, when the injurious force has been a compression of the chest or abdomen or merely a concussion, while not infrequently described, is still a rather unusual occurrence. However, Cutler and Beck¹ thought that rupture of the heart by contusion occurs more frequently than the reported examples would seem to indicate. The exact nature of the mechanism of this traumatic rupture, however, varies considerably, and would seem frequently to be doubtful. The case to be described is presented, therefore, first, because the lesions differ somewhat from others previously described, and second, because it is thought that the injury may be plainly accounted for by the nature of the mechanical force involved. I should also like to stress the point, in passing, that the medicolegal value of a correct differentiation of traumatic from nontraumatic rupture of the heart on the basis of anatomic observations is plainly very great, and that the not infrequent occurrence of the latter accident should be borne in mind.

REPORT OF CASE

History—J B, a white boy, aged 17, on Aug 13, 1929, while attempting to steal a ride on a truck, slipped off, falling to the ground. A rear wheel of the vehicle passed over his body. He was brought to the accident room of the New Haven Hospital, but was found dead on arrival. Abrasions were found over the upper part of the body, and blood was oozing from the nose and mouth. No family or past history was obtained.

Necropsy—Necropsy was performed approximately two hours after death. The body was seen to be that of a well nourished white boy, with a well developed bony and muscular structure, the weight was 50 Kg, and the height 162 cm. He did not, however, appear to be as old as his given age. His features were juvenile, hair on his face was scant and there was only a small amount of pubic hair. The external genitalia seemed rather underdeveloped. He was not, however,

Submitted for publication, Nov 7, 1929

* From the Department of Pathology, Yale University School of Medicine

1 Cutler, E C, and Beck, C S. *Surgery of the Heart and Pericardium*, Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1927, vol 4, p 273

overbese There was beginning postmortem rigidity of the extremities and jaws, with a postmortem lividity over the dorsum of the body The skin showed the following lesions on the left aspect of the upper lip, there was an abrasion measuring 3 cm in length and 1.5 cm in diameter There were also several other small abrasions and lacerations A small abrasion was seen on the lower lip and a small cut on its left side measuring 1.5 cm in length There were a number of superficial abrasions on the chin When the buccal mucosa was examined it was seen that the skin and underlying tissues had been stripped away from the mandible for a distance of several centimeters beginning about 2 to 3 cm from the right of the symphysis and extending back along the left mandible to a point about half way between the symphysis and the angle When the skin was reflected downward it was found that the bone was completely bared by this injury An ecchymotic area was seen over the right zygoma Superficial abrasions were seen on the neck, especially the right side, and on the chest, where they took the form of longitudinal striations measuring from 8 to 10 cm in length They extended downward and slightly laterally toward the left side of the body There was also seen a prominence of one of the left ribs, which was evidently broken and projected somewhat beneath the skin, but not through it On the abdomen above the left anterior superior iliac spine, there were seen several small blue or purple contusions Beneath one of these a small, hard mass was felt On dissection, this was seen to be a small piece of bone sharp at one end, blunt at the other, measuring 17 by 6 mm and evidently broken from the ilium, the border of which was irregular This fragment penetrated the deep fascia and lodged beneath the skin There was a moderate amount of hemorrhage in the adjacent tissue On the right knee, just below the patella, there was found an abrasion measuring from 4 to 5 cm by from 2 to 3 cm and a smaller one just distal to it Lymph nodes were felt in the right groin, but nowhere else

When the peritoneal cavity was opened, there was seen a large quantity of blood, amounting to several liters The peritoneal surfaces seemed smooth and glistening The bladder was contracted The edge of the liver was only a short distance below the costal margin on the right The blood apparently came from extensive injury to the spleen, which showed a number of deep lacerations Aside from these, the organ, which weighed 200 Gm and measured 14 by 8.5 by 2.5 cm was not remarkable

When the chest plate was removed, it was seen that each pleural cavity contained several hundred cubic centimeters of blood The transverse diameter of the heart and pericardium was 10 cm that of the chest 24 cm The pericardial sac was opened in situ and found to contain a small amount of fluid blood The pericardial surfaces were searched carefully for evidences of injury None was found laterally, inferiorly or anteriorly Posteriorly, however, there were found behind the right auricle, openings leading down into each pleural cavity, rather ragged in appearance and measuring from 2 to 4 cm in diameter The tears in the pleura reflected over the mediastinum were perhaps somewhat larger The lateral pleural surfaces seemed intact, smooth and glistening, though there were beneath them a few small areas of hemorrhage associated with fractured ribs, which were as follows on the right the second, third and fourth were broken in about the midaxillary line on the left, the fifth and sixth, slightly more anteriorly

The heart weighed 205 Gm It was firm in texture, contracted and evidently contained little or no blood The pericardial surface was smooth and glistening, except at the apex posteriorly, where a jagged laceration measuring 1.5 cm in diameter was found This lesion was situated in the left ventricle just lateral

to the interventricular septum, and opened directly into the left ventricle. There was also seen to be a small connection through the septum into the right ventricle, just about large enough to admit a probe. There was a rather narrow appearing fissure that led from the main rent laterally and slightly upward, in the left ventricle. Lying free in the pericardial sac was an irregular piece of cardiac tissue. This measured about 3.5 by 1.5 by 0.5 cm. On one small surface was subepicardial fat, which was somewhat torn. On another surface could be seen a small amount of endocardium, and a few fine columnae carneae. The other surfaces showed torn muscle fibers similar to those in the heart lesion itself. This portion of heart wall seemed obviously too small to fill the main opening in the ventricle completely, and seemed more likely to have come from the lateral more fissure-like laceration. No other fragments of cardiac musculature were found lying in the pericardial sac. It is probable that other pieces were torn loose, but were carried with the flow of blood out of the pericardial sac and through the pleural tears, into one of the pleural cavities, where, because of the large amount of blood, they were not observed. There was a small zone of subepicardial hemorrhage just above the rent in the heart, and extensive subepicardial hemorrhage and scattered petechial hemorrhage on the anterior surface of the left ventricle, with blotches of hemorrhage on the lateral surface. The subepicardial fat along the coronary arteries seemed somewhat increased. The arteries were not tortuous, and no obstructions could be demonstrated by probing. When the right side of the heart was opened, the endocardium was found smooth and glistening. Practically no blood was contained within. The foramen ovale was patent, connecting the two auricles by a small channel a few millimeters in diameter, which passed on a slant through the interauricular wall. The tricuspid valve measured 10 cm in circumference. The valve leaflets were thin and delicate. The chordae tendineae were thin and delicate and attached in their usual position. The columnae carneae and the papillary muscles of the right ventricle were neither flattened nor increased in size. The pulmonary valve measured 5.5 cm in circumference. The valve cusps were thin and delicate. The myocardium of the right ventricle seemed homogeneous and measured from 3 to 4 mm in thickness (exclusive of the columnae carneae). When the left side of the heart was opened, it was seen that just above the mitral valve, there was a tear in the endocardium of the auricle, which measured about 4 cm in length, and which extended down to the musculature, a few of the fibers of which were torn. There was no evident disturbance of the competence of the mitral valve due to this superficial lesion. That valve measured 7 cm in circumference, the valve leaflets being thin and delicate. The chordae tendineae were also delicate and attached in their usual position. The papillary muscles and the columnae carneae of the left ventricle were not increased in thickness or flattened. The ventricular wall was 12 mm thick. The aortic valve measured 5 cm in circumference. The valve cusps were thin and delicate. The aorta above was smooth and flexible, and otherwise not remarkable.

The remainder of the viscera will be described only briefly.

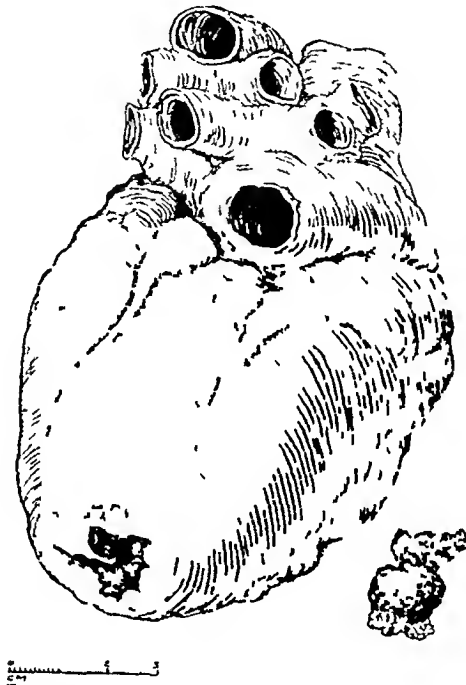
The right lung weighed 375 Gm, the left 275 Gm. Both showed a few small tears in the pleura, a few blebs of interstitial emphysema and blotches of subpleural hemorrhage.

The stomach and duodenum were not remarkable. The pancreas weighed 75 Gm and measured 16 cm in length. It was not unusual in appearance. The liver weighed 1,225 Gm, and measured 21.5 by 14.5 by 5.5 cm. The peritoneal surface seemed smooth, glistening and uninjured. At the base of the falciform

ligament, a small amount of extravasated blood was found beneath the capsule of Glisson, due to small, shallow tears in the hepatic substance. Otherwise, the liver was not remarkable.

The suprarenal glands together weighed 55 Gm, but showed nothing unusual. The cortex did not seem thinner than usual. The right kidney weighed 100 Gm, and measured 9.5 by 6 by 2.5 cm. The left weighed 125 Gm, and measured 10 by 6 by 2.5 cm. They were essentially normal in all particulars.

The bladder was contracted, and showed no pathologic change. The prostate was small and cut readily. The seminal vesicles were small and contained a small amount of yellow semigelatinous fluid. The testes together weighed 45 Gm. The tunica albuginea was not thickened. The substance was yellow, the tubules did not string out readily when pulled by forceps.



Traumatic rupture of the heart (posterior view). The small drawing shows the portion of the cardiac wall found loose.

The tongue, pharynx, larynx, trachea and esophagus were not unusual, except for numerous small hemorrhagic areas in the mucosa of the larynx and trachea. The thyroid gland weighed 40 Gm, and was not remarkable. The thymus weighed 62 Gm, and extended down over the great vessels. In the connective tissue capsule were some small extravasations of blood. It was light pink externally, and moderately soft. The cut surface appeared more yellow.

In the intestines, there was a well marked hyperplasia of Peyer's patches and of the solitary lymph follicles and of the lymph nodes in the mesentery. The lumen of the appendix was slightly dilated.

The bone-marrow was pink and of the consistency of fluid.

Beneath the scalp over the lower occipital region there was a hematoma measuring 6 cm in diameter but relatively thin, and containing only a small amount of blood. No fracture of the skull was found either externally or after removing the vault. In both orbital cavities, a slight amount of extravasated blood was

seen in the orbital fat. Beneath the dura covering the petrous portion of the temporal bone, there were small petechial hemorrhages. The pituitary gland was not unusual. The brain showed nothing of note externally except a slight flattening of the right hemisphere, probably artefact. Multiple frontal sections revealed nothing of note. The spinal cord was not remarkable either externally or on section.

Microscopic Observations—Heart. The muscle fibers of both ventricles were not unusual in size or staining properties. A section of the edge of the lacerated region of the apex showed no evidence of unusual cellular infiltrations, and the muscle fibers appeared well preserved. Small extravasations of red blood cells were seen in the tissues adjacent to the torn edge. In scattered areas, likewise, through the left ventricle, small hemorrhages were seen in the connective tissue septums and in the fatty tissue of the epicardium. The fibrous tissue of the heart was not increased, and the blood vessels showed no changes.

Other Organs. A few scattered and clumped red blood cells were seen in the alveoli of the lungs, otherwise, there were no unusual changes. A section through an uninjured area of the spleen showed no changes of note. Postmortem changes were found in the mucosa of the stomach. The other layers were not remarkable.

The pancreas, liver, suprarenal glands, kidneys and bladder presented no microscopic changes of interest.

The alveoli of the prostate were fairly numerous, but small, and the stroma surrounding some of them presented a few scattered small round cells. Spermatogenesis in the tubules of the testes was only moderate with few mature sperms visible.

The structure of the thyroid gland was not remarkable. The lobulation of the thymus was well marked. The cortical and medullary portions were fairly distinct. In the central portion of almost every lobule was seen at least one large rounded, pink-staining mass without any definite structure. Hassall's bodies seemed somewhat fewer than usual. Mitotic figures were seen fairly frequently in the medullary portions of the gland.

The aorta was not unusual.

Postmortem changes were present in the mucosa of the ileum. Peyer's patches were hyperplastic with prominent germinal centers, though only moderately numerous mitoses. The lymphoid tissue of the appendix was prominent, the lumen was dilated. The follicular structure of the lymph nodes was seen, but the central portions of the nodes were loosely arranged and rather acellular.

Both the pars nervosa and the pars glandularis of the pituitary gland were well stained and preserved. The arachnoid was somewhat thickened. There was great congestion of the pial vessels and of those of the ependyma of the ventricles. The spinal cord showed nothing of note.

COMMENT

It would seem from the distribution of the injuries in this boy that the wheel of the truck in passing over his body struck first the region of the right shoulder, then passed over his chin, in a glancing manner, thus stripping the soft tissues from the mandible as described. It then rolled on over the chest in a course downward and from right to left and over the left side of the abdomen, severely compressing the chest and abdomen with resulting fracture of several ribs and rupture of the spleen. That more ribs were not broken was undoubtedly due to

the fact that because of youth the chest was flexible, and bent in under the weight of the vehicle, springing back into position after it had passed. The compression was sufficient, apparently, to tear loose a portion of the attachment of the mediastinum, opening channels between the pericardial and the pleural cavities. The passage of the wheel over the great blood vessels prevented the outflow of blood from the pulmonary artery and aorta. The heart was probably dilated from the physical exertion employed in running and attempting to board the truck. As the wheel passed on downward the blood was forced toward the apex of the heart, and the strain on the musculature was intense. The wall ruptured in that region, which was also the thinnest part of the left ventricle. The force was so great that a portion of the wall was actually blown completely out of the heart as a plug of tissue. The fact that the semilunar valves were not damaged may indicate that the compression acted to force the blood in the aorta and pulmonary artery away from the heart. In regard to the pleural rents, it might be argued that the force of escaping blood from the heart so distended the pericardium that it ruptured with a tearing likewise of the pleurae, allowing the blood to escape thus. On the other hand, it seems more likely that the openings were caused by the distortion accompanying the compression. If the former had been true, it would seem as if there should have been much more extravasation of blood in the mediastinal tissues than was actually present. Cessation of the heart action presumably took place a few seconds or, at most, minutes from the time of the accident, the immediate cause of death being probably exsanguination. This differs from the mechanism in a spontaneous rupture of the heart associated with an infarct, gumma or aneurysm, in which the accumulation of blood in the pericardial sac finally so embarrasses its action that the organ soon ceases to beat. It is conceivable that a traumatic rupture of the heart, less extensive in degree than the one described, might be compatible with life, provided that the rent became filled with clotted blood before too much had been lost. The accumulation in the pericardium would flow off into the pleural sacs, and the heart be thus spared its effect. This fact has been brought forth a number of times in discussions of puncture wounds of the heart and pericardium, in cases in which the patient has survived the accident. In this case, it is obvious that the fractured ribs themselves played no part in the trauma to the heart or even to the pericardium because of their distance from the lesions.

The relation between the rupture of the heart and the general physical condition is interesting to consider. The underdeveloped sex characteristics seen in this youth and the hyperplasia of thymus and lymphoid tissue are characteristic of so-called status thymicolymphaticus. A weakness and softness of the cardiac musculature are described as occurring

in that condition. It might be felt by some that this played a rôle in the production of the lesion. Even if one were to admit that there is such a definite entity as status lymphaticus, which is questioned by many authorities, it would seem unnecessary to call on that to aid in the explanation of the present case, as the force would seem sufficient to have caused the damage in a sound organ.

Many of the other instances of traumatic rupture of the heart to be found described in medical literature are much less capable of a definite explanation as regards the mode of production than the one here described. Saphir² reported the case of a child, aged 4, over whom a motor truck passed with no apparent injury to the chest and but few abrasions on the abdomen. The heart showed a rupture transversely from the midportion of the anterior surface of the left ventricle, across the left margin ending in the lower third of the posterior surface of the left ventricle near the interventricular septum. The tear measured about 6.5 cm. in length. Microscopically, the cardiac musculature showed no degeneration, fibrosis or inflammatory reaction. The right pubic and iliac bones were the seats of fractures with hemorrhage into the adjoining fascia and the peritoneal cavity. In this child, the thymus weighed 30 Gm., and the mediastinal, peritoneal and retroperitoneal lymph nodes were enlarged. The aorta, however, showed no hypoplasia. He felt that a status lymphaticus was not present despite these appearances. His explanation of the rupture was that it was due to trauma with the greatest force acting in the region of the right pelvis. He did not explain how this force actually produced the lesion, and he stated that spontaneous rupture could not be absolutely excluded. Turner and Gould³ described an accident in which a 47 year old sailor fell a distance of 20 feet (6 meters) apparently landing on his head. He lived five hours after entrance into the hospital. Aside from a few superficial bruises and lacerations on the face, scalp and hips the only gross injury to the body was a fracture of the first segment of the gladiolus. There was no tear in the parietal pericardium. A small extravasation of blood was seen in the anterior mediastinum and about 450 cc of blood in the pericardial sac. The right side of the heart was collapsed. The cardiac musculature appeared normal and healthy, aside from a small tear found in the anterior wall of the right ventricle close to the semilunar valves, large enough to admit a lead pencil into the ventricular cavity. They thought that the fracture of the sternum was due to indirect violence, the result of sudden flexure of the spine, with an accompanying pressure on the heart, and the production of a small

2 Saphir, O. Rupture of the Heart by Indirect Trauma in a Four Year Old Boy, *Am J M Sc* **173** 353, 1927

3 Turner, G. R. and Gould, L. P. A Case of Traumatic Rupture of the Heart, *Lancet* **2** 567, 1917

opening From the clinical observations, they felt that there was an initial slight hemopericardium, with the formation of a clot in the opening This later dislodged and the sudden distention of the pericardium with blood caused death A case reported by Howat⁴ is somewhat similar A healthy shipwright, aged 23, fell 45 feet (14 meters) landing on some wooden planks and steel plates He was found dead on his arrival at the hospital, twenty minutes later A few scratches and bruises were found at the right elbow, but no other gross external injuries Lacerations were found in the liver with fluid blood in the peritoneal cavity and an extravasation into the retroperitoneal tissue from lacerations of the right kidney Blood was also seen in the loose tissue of the posterior mediastinum The pericardium was intact, with about 750 cc of blood contained within the sac A slitlike opening was found leading into the cavity of the left auricle situated exactly in the free edge of the auricular appendage, and measuring about 0.25 cm in length Microscopic sections showed no cardiac disease Howat felt that traumatic rupture of the heart within an intact pericardium is almost certainly due either to compression or to concussion The former may act either by directly bruising the heart tissue so that the injured part gives way immediately, or later, or else without this direct injury, by so increasing the intracardiac blood pressure that the healthy heart wall is burst from within In this particular instance, he felt that the blood pressure increase on a distended auricle was such as to drive the contained blood away from the natural orifices toward the blind extremity of the auricular appendage The part played by concussion here is not certain He cited another instance of a 68 year old brick layer who had his chest compressed dying five weeks later with a rupture of the heart near the apex through a bruised area, of which there were several No other cardiac lesion was found He thought that this is an example of the delayed effect of traumatic injury of the heart Traumatic rupture of the heart with uninjured chest wall was reported by Kellert,⁵ who said that a 44 year old Italian workman was caught in a cave-in of a sand bank and buried to his waist He was dead when dug out The autopsy was performed eight days later on the embalmed body Over the anterior aspect of the chest, especially on the left, were five small abrasions, while below both knees were likewise abrasions No fractures were in evidence The peritoneal cavity contained approximately 1 liter (1,000 cc) of bloody formaldehyde-containing fluid The left pleural cavity contained a large amount of fluid, and clotted blood, 1,800 cc in all, with a compression of the lung into the upper portion of the cavity In the pericardium was a large amount of firm blood clot

4 Howat, R. K. Traumatic Rupture of the Heart *Lancet* **1** 1313 1920

5 Kellert, E. Traumatic Rupture of the Heart Report of a Case with Uninjured Chest Wall, *J. Lab. & Clin. Med.* **2** 726 1917

surrounding the heart and adherent to the pericardial surfaces. The lower left portion of the pericardial sac presented a ragged opening, 4 cm in diameter, which was filled with firm, friable blood clot, and communicated with the left pleural cavity. The heart weighed 370 Gm. Near the apex on the right posterior surface was a ragged linear laceration of the heart wall measuring 5 cm in length, communicating with both ventricles, the laceration extending across the interventricular septum. Just beneath the right auricle were two minute openings in the fat and myocardium. In the left ventricular wall beneath the auricular appendage was a transverse laceration in the heart muscle, 2.5 cm long. The papillary muscles of the right ventricle were lacerated, the portion attached to the chordae tendineae being found free in the auricle. The endocardium of the auricle above the tricuspid valve was lacerated. The papillary muscles of the left ventricle were likewise torn from their attachment to the cardiac wall. The aorta at its origin was separated through one half of its circumference. Microscopically, there was a slight amount of fatty infiltration of the right ventricular wall and vacuolization in the muscle fibers with increased amount of pigment about the nuclei, which varied greatly in size. An occasional area of fibrosis and a rare focal accumulation of lymphocytes, endothelial cells and polymorphonuclear leukocytes were seen. Kellert suggested two possibilities to explain the origin of the lesions. One is that the weight of the falling earth, which was soft and compressible, caused equal pressure over the chest resulting in great compression and bursting of the heart, much as though a rubber bag distended with fluid were compressed at its middle. He thought, however, that such an effect without fracture of the sternum or ribs was unlikely. The second explanation, which he felt was more probable, is that the large quantity of sand around the lower part of the body exerted such pressure that most of the blood was driven out of the vessels with a resulting overdistention of the heart and multiple rupture. It was his opinion that the ruptured pericardium was an indication of the greatness of the intracardiac force, and that the pathologic changes in the heart, though slight, probably contributed to the severity of the injury.

Kellert quoted a number of other articles describing traumatic rupture of the heart. One is described by DuFour,⁶ in which a 13 year old girl underwent severe compression of the thorax and strangulation. There was no wound of the chest wall or pericardium, but a rupture of the right auricle. McOscar and Voelcher⁷ cited the case of a man

6 DuFour. Rupture de l'oreillette droit par compression du thorax combinée avec la strangulation à l'aide des mains, *Ann d'hyg* **16** 185, 1911

7 McOscar, J, and Voelcher, A. On a Case of Traumatic Rupture of the Interventricular Septum, *Tr Path Soc London* **48** 47, 1896-1897

who died eight days after being run over by a wagon. No fractures of ribs or sternum were found but a transverse rupture of the ventricular septum 2.5 cm in length. O'Neill⁸ reported a boy 9 years old who was knocked down and jumped on by other boys. He walked home, but died at the end of eight days. A hematopericardium was found and a small rupture at the auriculoventricular junction of the left side of the heart. No wounds of the chest were mentioned. The case of a man, aged 44 who was struck by a heavy weight and died forty-two hours later, was cited by Kugel.⁹ A hematopericardium and a sharp tear in the right ventricle were found. The heart was enlarged and fatty masses were present on the surfaces of both ventricles. No fractures were present. Robertson¹⁰ gave the case of a 49 year old man who fell from a railroad carriage hitting his left shoulder on the ground. Death occurred forty-five minutes later. No wounds of the chest were present. The pericardium was intact, but there was a rent 3.1 cm long in the left ventricle. Gibbons¹¹ told of a coolie who died three hours after being struck over the chest and elsewhere by a bamboo stick. No penetrating wounds were present. The heart, however, presented a rupture at the apex communicating with the right ventricle. Hutchinson¹² described a rupture of the right ventricle caused by a kick on the chest from a horse. The man died fourteen hours after the injury. There was no break in the skin of the chest. A tear in the pericardium anteriorly and a rupture at the apex of the right ventricle were revealed by necropsy. Groom¹³ wrote of a boy aged 16 who was caught between the shaft of a pony cart and a wooden railing. Death took place one month later. A rupture 2.5 cm long in the posterior portion of the left ventricular wall in an aneurysmal dilatation was found at necropsy. The trauma probably weakened the wall of the heart allowing the production of the aneurysm which later broke. Peacock¹⁴ gave the story of an athlete, 25 years of age, who was struck a blow in the epigastrium and died forty minutes later, a laceration 8.75 cm long being found in the right ventricle.

8 O'Neill, B. J. A Case of Traumatic Rupture of the Heart. *J. A. M. A.* **62** 697 (Feb. 28) 1914.

9 Kugel, A. Ein Fall von Herzruptur, *Prag med. Wchnschr.* **34** 303, 1909.

10 Robertson, C. Note on a Case of Rupture of the Heart, *Lancet* **1** 240, 1897.

11 Gibbons, J. B. Rupture of the Heart by a Blow with a Stick. Survival for Over Three Hours, *Indian M. Gaz.* **32** 443 1897.

12 Hutchinson, F. Case of Traumatic Rupture of the Heart, *Brit. M. J.* **2** 1427, 1894.

13 Groom, W. A Case of Rupture of the Heart, *Lancet* **1** 1202 1897.

14 Peacock, T. B. Case of Rupture of the Right Ventricle of the Heart. *Tr. Path. Soc. London* **31** 72 1880.

There have been still other reports of traumatic cardiac rupture, among which is that of Godlee¹⁵ who mentioned a case of rupture of the right ventricle likewise caused by a blow of the fist, in this instance on the precordium. Stephens¹⁶ cited the case of a healthy boy aged 16, who suffered a compression of his abdomen and chest by a heavy steel tube which was being lowered by a crane. He stepped back a few paces and fell dead. Postmortem examination showed a pericardial sac full of blood and a tear 2.5 cm. long in the right ventricle. Stephens raised the question as to whether this was produced by the back pressure caused by the tube against the abdomen. Bilderbeck¹⁷ reported the instance of a soldier, 19 years old, who was caught between the cross-bar handle of a wheeled fire pump and a stone wall. The blow struck him across the middle of the chest. He was seen to fall dead at once. Postmortem examination showed some slight contusions and cuts about the head but no fractures or other serious external lesions. The ribs were pliable, so that it appeared as if the chest could be easily compressed. The pericardium was full of blood but undamaged. The heart was small and the valves and musculature were apparently normal with no trace of old disease process. In the right auricular wall between the right coronary artery and the entrance of the inferior vena cava was a small rent measuring about 1.9 by 1.25 cm. Bilderbeck believed that at the moment of the accident, the man took a deep inspiration, engorging the right auricle which then burst on the sudden compression of the costal wall. Kennedy¹⁸ reported the case of a woman between 60 and 70 years of age who was knocked down by a cart, dying about one hour later. No bruises were found externally, but several ribs were found broken, as well as the sternum, though the parietal pericardium was not injured. About 300 cc. of blood was contained within the sac. In the anterior wall of the left ventricle, there were two ruptures half an inch apart extending across the wall a short distance below the auriculoventricular groove. The upper wound measured 3.75 cm. on its epicardial surface, but on its endocardial surface only about 1.7 cm. The lower wound was 1.25 cm. long. Both were ragged. The heart musculature was soft and pale, and microscopically there was some brown atrophy but not excessive for her age. Kennedy felt that in view of the small amount of coronary disease and the character of the wounds, the mechanism of production of the lesions was rupture by bursting.

15 Godlee, R. J. The Repair of Wounds of the Pericardium and Heart, *Oxford Surgery* 4 173, 1918.

16 Stephens, G. A. Three Thoracic Emergencies *Lancet* 2 1382, 1922.

17 Bilderbeck, A. C. S. Traumatic Rupture of the Heart without Fracture or External Lesions *Brit. M. J.* 1 675, 1919.

18 Kennedy, A. M. Rupture of the Heart by External Violence, *Lancet* 7 105, 1914.

Heger-Houbotte¹⁹ described two cases, the first of a man who fell 30 meters sustaining only rather superficial external lesions, but a fracture of three ribs. There was an extensive rent in the right auricle and ventricle and the septums between the right and left sides of the heart. He thought that the fracture of the ribs could explain the ruptures. The second case was that of a chauffeur who was thrown violently from a car, dying instantly. The external lesions were not significant. The right ventricle showed a star-shaped wound near the tip on the posterior surface. He felt that the heart was forced against the vertebral column and the ventricle ruptured from the pressure of the blood.

Schutt²⁰ cited an accident in which a 41 year old man suffered a marked compression of the chest between two heavily laden automobiles and died immediately. External wounds were slight. Fractures of several ribs were found anteriorly near the sternum and posteriorly near the vertebral column. The pericardial sac contained about 250 cc of blood, for the most part fluid. A few hemorrhagic areas were seen in the mediastinum. A tear, 20 cm long, was present in the pericardium near the junction of the mediastinum and diaphragm. The heart showed extensive tears, in the right ventricle, pulmonary artery, aorta and left ventricle, with ecchymotic areas on the posterior aspect of the latter. It was Schutt's opinion that the force acted from the region of the right shoulder downward and posteriorly causing the fracture of the ribs and exerting a downward pull on the heart, tearing the pulmonary artery and aorta and causing the wounds in the heart itself, ripping the pericardium and bruising the posterior aspect of the left ventricle against the vertebral column. He stated that cases of traumatic rupture of the heart can be grouped into those with a bursting rupture (*Platzruptur*) and those with a rupture due to a twist (*Zerungsruptur*). He quoted Jaffe²¹ to the effect that the former is due to an explosive action through hydraulic pressure, while the latter is associated with a compression or distortion which causes a tear in the region most severely pressed on.

CONCLUSIONS

This case differs from the cases reported in the literature reviewed, inasmuch as it is the only one in which the actual extrusion of a portion of cardiac wall was observed. The latter fact would seem to be strong evidence of a bursting due to increased intracardiac pressure.

19 Heger-Houbotte, M. Rupture traumatique du coeur, *Arch internat de med leg* **2** 292, 1912.

20 Schutt, W. Ueber einen Fall von Traumatischer Herzruptur nach Brustquetschung, *Centralbl f allg Path u path Anat* **31** 169, 1920.

21 Jaffé, R. Sprengung des linken Ventrikels durch Pufferverletzung, *Munchen med Wchnschr* **64** 742, 1917.

In this instance, likewise, the manner of application of the force producing the lesion seems evident. In many of the other instances described in the literature, the trauma was more indirect, and one often wonders just how the damage was brought about. Cutler and Beck¹ who were quoted at the beginning of this article felt that the mechanism of contrecoup may play a part, but the compressibility of the thoracic wall, combined with the toughness of the pericardium as compared with the friability of the cardiac muscle, makes it evident that the heart may be damaged without a tear in the pericardium. That a great increase of intracardiac pressure may produce a rupture of an apparently healthy heart would seem true. Whether or not sufficient pressure can be caused by forcing the blood from the lower extremities and perhaps partially from the abdominal viscera as suggested by Kellert is difficult to decide. Animal experimentation might help solve the problem. The effect of concussion in producing ruptures of the liver, spleen and mesentery has frequently been observed and discussed and it does not seem illogical to suppose that the effect on the heart might be the same. In several of the cases, reports of which have been cited here, there was some indication that the myocardium had suffered some previous, unrelated damage which undoubtedly was a contributing factor in the production and extent of the injury to the hearts. Strong advocates of status thymicolymphaticus might hold that in the instance here described there was a predisposing factor of weakness of the cardiac musculature. It is difficult either to deny or to prove this.

I draw the conclusions from my case and others reported that traumatic rupture of the heart may be brought about by (1) great increase of intracardiac pressure, (2) concussion or direct compression acting on the heart to cause immediate tears or bruises which later give rise to perforations.

MYCOTIC ANEURYSM OF THE SUPERIOR MESEN- TERIC ARTERY COMPLICATING BACTERIAL ENDOCARDITIS

REPORT OF THREE CASES *

FERDINAND C HELWIG, M D

AND

ELLIS W WILHELMY, M D

KANSAS CITY, MO

Mycotic aneurysm is a relatively infrequent complication of bacterial endocarditis. A lesion of this type involving the superior mesenteric artery and its branches has been reported in but twenty-five of all the case reports which have been compiled. Localization in the superior mesenteric artery is considered by Aschoff¹ to be next in infrequency to that in the coronary artery. Von Schrotter² found only one instance of involvement of this vessel in 19,300 autopsies. Leaflet and aortic lesions are the most frequently reported, and multiple aneurysms have been encountered on a few occasions.

Since we are discussing only those aneurysms of which intravascular bacterial infection is the cause, only the theories in regard to the production of this type of lesion will be considered. The most frequent predisposing factor in the formation of these lesions is bacterial endocarditis, although septicemia, from any cause, may be the source.

Stengel and Wolferth³ mentioned three methods by which the process develops: (1) lodgment of infected emboli in the lumina of the vessels, or vasa vasorum, (2) the settling of bacteria on the inner surface of the vessel or vasa vasorum (this being the case only in the heart and aorta), and (3) by the continuity, or contiguity, of infection of the aortic or pulmonic valve.

In the mesenteric artery, most of the aneurysms are doubtless embolic, and in vessels of this caliber they are probably due to infected

Submitted for publication, Nov. 7, 1929.

* From the Departments of Pathology and Internal Medicine, St. Luke's Hospital.

1 Aschoff, cited by Kolm, L. Zur Kenntnis der Anatomie, Klinik und Therapie des Aneurysma der Arteriae mesentericae superioris, *Arch. f. klin. Chir.* **123** 684 (March) 1923.

2 Von Schrotter. Erkrankung der Gefasse, in Nothnagel's *spezielle Pathologie und Therapie*, 1901, vol. 15 p. 271.

3 Stengel and Wolferth. Mycotic Aneurysms of Intravascular Origin, *Arch. Int. Med.* **31** 527 (April) 1923.

material being held in contact with the vascular intima by angulation, bifurcation or immediate narrowing.

Eppinger⁴ was of the opinion that the infection is set up first in the adventitia, and involves the media and intima secondarily. However, Benda,⁴ Unger⁴ and many others felt that the process is primarily an endothelial injury, with subsequent involvement of the other coats, and explained the progress of the lesion as follows. With the contact of infected material and subsequent endothelial necrosis, the wall becomes progressively involved, pressure pounding on this weak surface produces dilatation and subsequent outpouching of the vessel wall.

Klotz has shown that both intima and adventitia may be involved at the same time, the former through the lodgment of the septic emboli in the lumen, the latter through bacterial embolism in a devitalized wall through the vasa vasorum.

Microscopic study of the aneurysms in our cases shows that they were probably produced in the manner explained by Benda⁴ and Unger⁴.

REPORT OF CASE

CASE 1—History—A 16 year old boy had been sick for a week with soreness and pain in the abdomen which was worse around the umbilicus, when first noticed, but at the time of examination was most severe in the right lower quadrant. The initial attack came on after the patient had eaten breakfast, and was accompanied by twenty-four hours of vomiting and bloody mucous in the stools. The patient's past history revealed that he had had diphtheria when he was 4 years old and acute inflammatory rheumatism when he was 9. During the latter illness, "almost every joint in his body" was involved at some time. He had a tonsillectomy one year previous to entry, because of numerous attacks of tonsillitis. Not long after this, he noticed that he was tired and worn out all the time, and was told by a physician that he had heart disease. A few months later, he had an attack of acute abdominal pain in the left side, which remained "sore" up to the time he entered the hospital. He had had some dyspnea on exertion, but not palpitation or edema.

Physical Examination—On examination, he appeared pale and sick. The heart was markedly enlarged. The left base extended to the axillary line and the point of maximum impulse was in the fifth interspace and about one-half inch (1.27 cm.) outside the midclavicular line. Both a systolic murmur and a diastolic murmur were present, the latter was loud and heard over the aortic area. The abdomen was tense and tender, and rigid over the right rectus muscle. There was slight clubbing of the fingers. The urine was loaded with bacteria, pus and albumin. The red blood cell count and the hemoglobin content were essentially normal, but there was a leukocytosis of 32,000, 84 per cent of the cells being polymorphonuclear neutrophils.

Course—Vomiting persisted intermittently throughout the entire course of the illness. One week after admission, the patient had sixteen clonic convulsions in twenty-four hours, and a firm, tender, pulsating mass was felt in the upper left epigastric region.

⁴ Eppinger, Benda, Unger, Klotz, cited by Stengel and Wolfeith (foot-note 3).

Necropsy (by Dr Watson Campbell) —Some blood-tinged fluid was seen in the peritoneal cavity. A massive retroperitoneal hemorrhage originating in an eroded hemorrhagic infarct near the pelvis of the right kidney was encountered. This had almost completely decapsulated the kidney. There was a large mass, the size of an orange, in the mesentery, which was found to be a mycotic aneurysm of the superior mesenteric artery. It was filled with a laminated thrombus. Infarcts were found in the spleen and the kidneys. There were large and small vegetations on the mitral valve. Just below the aortic valve, on the mural endocardium, there was a large vegetation.



A large mycotic aneurysm of the superior mesenteric artery with laminated thrombus (case 1). A probe is seen in the lumen of the artery leading into the aneurysmal sac.

CASE 2—History—A white man, 41 years old who had been ill for three months complained of weakness, night sweats and fever. He had lost 45 pounds (20.4 Kg) in weight, and was having frequent attacks of pain throughout the abdomen, particularly under the left costal margin. The patient's past history was negative for rheumatic fever, infectious diseases of childhood and focal infection.

Physical Examination—On examination, the patient was pale and anemic. His temperature was 102.8 F (39.4 C), pulse rate 120, and blood pressure,

132 systolic and 86 diastolic. His heart was slightly enlarged and extended 12 cm to the left of the midsternal line. There was rather marked heaving of the apex in the fifth interspace 2 cm outside the midclavicular line. A loud blowing systolic murmur could be heard over the entire precordium more marked over the apex. The abdomen was tender and rigid over the right rectus from the costal margin to the pubis most marked in the region of the umbilicus. There were 3 680 000 red blood cells and 12 000 leukocytes. The hemoglobin content was 65 per cent. Small quantities of albumin and occasional red cells and casts were found in the urine. A pure growth of *Streptococcus viridans* was isolated from the blood.

Course—The patient grew progressively worse and four months after the first examination began to show petechiae in the conjunctiva and buccal mucosa. The attacks of pain in the abdomen and splenic region became an almost daily occurrence and during the last month of his life he suffered blindness of one eye with severe headache and a few days later a slow progressive hemiplegia and died.

Comment—One interesting feature about this case was the fact that several times after a severe attack of abdominal pain, obviously due to emboli in the visceral vessels the patient would have the typical symptoms and the physical appearances of intestinal obstruction which would clear up after from twenty-four to forty-eight hours.

Necropsy—Anemia and emaciation were marked. Petechiae were scattered diffusely over the entire skin and in all the visible mucous membranes. The heart weighed 272 Gm and was flabby. The mitral valve was encrusted with large fresh vegetations, which extended up onto the auricular wall and involved the mitral leaflet of the aortic valve. Small vegetations were present on the corpus arantii of each aortic cusp. The spleen and the kidneys were peppered with white infarcts of varying size. Many were healed and in the spleen some of these infarcts had undergone abscess formation. There was a small, round mass in the mesentery to which was attached a Meckel's diverticulum. On careful examination, this mass was found to be a small mycotic aneurysm of one of the branches of the superior mesenteric artery. It measured 25 mm in diameter and on cross section was completely filled with a typical laminated thrombus.

CASE 3—History—A woman 38 years old was suddenly stricken with numbness in the feet and legs and was unable to walk for an hour. Three months later she presented dyspnea on exertion swelling of the feet and ankles, and pain over the left kidney. She lost 25 pounds (11.3 Kg) in weight.

Physical Examination—On examination, seven months after the onset of the illness the patient was anemic and emaciated and there was impairment of vision in the right eye. The conjunctivae were dotted with petechial hemorrhages. The heart was of about normal size. A loud systolic murmur was heard over the apex, and was transmitted to the axilla. Examination of the upper part of the abdomen was unsatisfactory because of marked tenderness and rigidity in the right hypochondriac region. There was marked tenderness over the area of the right kidney. The spleen could not be felt. The feet and the ankles were edematous. *Streptococcus viridans* was obtained repeatedly in blood cultures. The urine contained a large amount of pus and red cells on all examinations. The leukocyte count was 21 600. There was marked secondary anemia that grew progressively worse.

Course—One week after admission the patient presented marked edema of the feet and legs and subsequently all the symptoms and observations of severe cardiac failure. She died four weeks after admission.

Necropsy—Marked anemia was present, and petechial hemorrhages were found in the conjunctiva and in the skin over the knees. The spleen contained many anemic infarcts, some showing abscess formation. The kidneys were riddled with variable-sized healed and anemic infarcts, and there was an acute hemorrhagic nephritis superimposed. A large mycotic aneurysm of the superior mesenteric artery, measuring 9 by 5.5 by 5 cm, was found in the mesentery. It was partially filled with a laminated thrombus and red clots, and its walls were as much as 12 mm thick. The heart weighed 275 Gm, and the mitral valve was covered with thick vegetations and the leaflets were badly ulcerated. These vegetations had extended as far as 3.5 cm on the mural endocardium of the left auricle, and down onto the chorda tendineae of the mitral leaflets. Other observations were of no particular interest.

CLINICAL COMMENT

In view of the fact that in most cases bacterial endocarditis demonstrates embolic phenomena for months before death it is surprising that mycotic aneurysms of the mesenteric vessels are not far more prevalent than one would be led to believe from a review of the literature.

However, since in many cases the aneurysm is small and the lumen well filled with a laminated thrombus so that pulsation is slight (as in our case 2) and rigidity and tenderness make abdominal examination unsatisfactory, it is not surprising that so few cases can be diagnosed clinically.

The patient in case 1 lived for six weeks during the development of the tumor, on finding a movable pulsating mass not connected with the aorta, Dr. Campbell made the clinical diagnosis of mycotic aneurysm of the mesenteric artery.

In cases 1 and 2 an attack of abdominal pain, followed by nausea and vomiting, rigidity and tenderness, distention and obstipation marked the onset of the trouble. In case 3 there were no symptoms referable to abdominal pathologic conditions and though this tumor was almost as large as an orange, the finding of it was entirely a matter of post-mortem enlightenment, as the finding of most of these aneurysms is.

The rapidity with which the tumor develops is, of course, largely dependent on the surrounding structures and the amount of pressure that is placed on the weakened surface of the blood vessel. As can be seen from an examination of the clinical histories in these cases two of the aneurysms in the main stem of the mesenteric artery developed into remarkably large tumors in the short period of from three to five weeks while the aneurysm in case 2 was small, and as nearly as could be determined from the history had apparently been developing twice as long as those in the other cases.

The erosive nature of these lesions naturally predisposes the blood vessel to rupture, but this complication was not encountered in this small series.

Although intracranial aneurysm of this type was not diagnosed clinically, it should have been suspected in case 2 because of the slowly progressing neurologic symptoms. However, a differentiation from embolism with thrombus formation would have been largely speculative. Unfortunately, no autopsy on the brain could be obtained.

It is interesting to note that, although small vegetations were continuously being carried away from the leaflets by the vascular circulation in these cases, not one showed multiple aneurysms. This fact merely bears out the known contention that the endothelium of the vascular system is resistant, in all probability infection can get a foothold only when the nature of the vessel is such that the infected emboli are held in contact with the wall over a period of time. Several times, in case 2, emboli lodged in the superficial vessels, causing marked tenderness, severe pain and swelling, but on each occasion the processes subsided after three or four days. One particularly painful lesion was in the palm of the right hand, but this, like the others, cleared up in about a week.

CONCLUSIONS

Three cases of mycotic aneurysm of the superior mesenteric artery complicating bacterial endocarditis are reported. Only one was diagnosed clinically. None of these aneurysms ruptured. Multiple lesions were not found. The finding of three cases in a small series suggests that they are frequently overlooked.

PRIMARY SQUAMOUS CELL CARCINOMA OF THE VAGINA COMPLICATING LATE PREGNANCY IN A PATIENT SIXTEEN YEARS OLD*

LOUIS TUFT, M.D.

Pathologist, Northwestern General Hospital

PHILADELPHIA

The case here reported is described because it illustrates the occurrence of a tumor which is uncommon in an extremely youthful person and which is a rather rare complication of pregnancy

REPORT OF CASE

The patient, a negress, aged 16, was admitted to the wards of the Northwestern General Hospital, in the service of Dr Van Dolsen, Dec 28, 1928, on account of vaginal bleeding, abdominal enlargement, leukorrhea and abdominal pain. The last menstrual period had begun on May 25, 1928, since then, the abdomen had become progressively larger. In the latter part of November, 1928, the patient began to pass blood in the form of clots from the vagina, this continued until the time of admission. She had lost about 20 pounds (9 Kg) since October otherwise, her history was unimportant. Prior to admission, she had been a patient in another hospital, where her symptoms had been diagnosed as due to fibroid tumor. The patient was married in July, 1928, but admitted that she had had sexual relations at least two years previously. She said that intercourse was never painful, and that slight leukorrhea had been present as long as she could remember.

Examination on admission showed a moderately well nourished young woman. The results of the examination were essentially negative, except for the external signs of pregnancy and the enlargement of the uterus to a point above the umbilicus. On vaginal examination, a cauliflower-like growth was seen and felt involving the upper two thirds of the posterior vaginal wall, extending to the posterior culdesac, but not invading either the cervix or the anterior vaginal wall. The cervix was soft and admitted one finger. There was some involvement of the anterior wall of the rectum, but as yet no breaking through of the mucosa. The growth was friable and bled easily. The urine on admission showed from 1 to 2 red blood cells per high power field, and from 3 to 5 white blood cells per high power field. These cells increased markedly in number as the condition progressed. The blood count showed hemoglobin, 74 per cent, red blood cells, 4,020,000, white blood cells, 16,650, polymorphonuclears, 87 per cent, small lymphocytes, 12 per cent, and eosinophils, 1 per cent. Both the Kolmer and the Kahn serologic tests for syphilis were negative. The values of blood sugar and urea were normal.

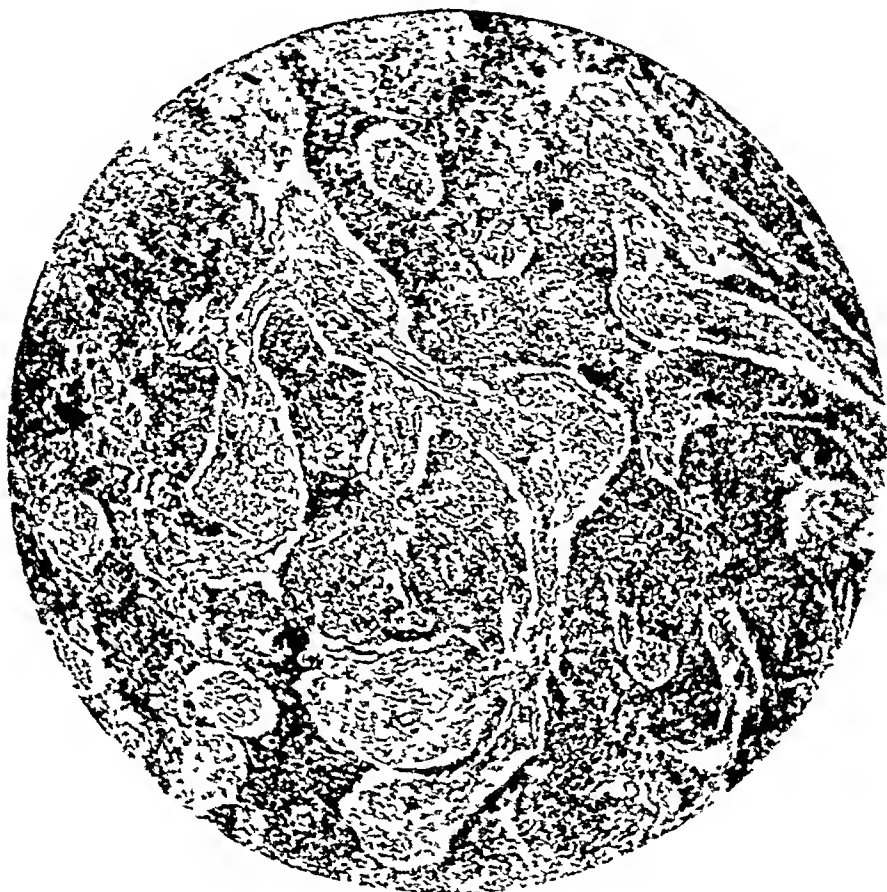
On December 22, a biopsy was done, a small portion of the growth being examined histologically (see accompanying photomicrograph) and reported on as follows. Section showed large numbers of islands or nests of squamous epithelial

* Submitted for publication, Nov 14, 1929

† From the Laboratories of the Northwestern General Hospital

‡ Read before the Philadelphia Pathological Society, Oct 10, 1929

cells, growing in and invading in an irregular fashion a stroma consisting of fibrous connective tissue and containing large numbers of small round cells, plasma cells and a few polymorphonuclear leukocytes. The tumor cells showed only a slight tendency to differentiation, with the formation of epithelial pearls. The nuclei of these cells were large and hyperchromatic and showed numerous mitoses. A diagnosis of squamous cell carcinoma was made. The source of this tumor from the history, could only be the squamous epithelium of either the vagina or the cervix. Since the latter was free it must have arisen primarily from the vagina.



Section of primary squamous cell carcinoma of the vagina

On Dec 26, 1928, 30 mg of radium was implanted by means of needles into the mass on the posterior vaginal wall. Following this implantation, bleeding lessened considerably. On December 29, because the child seemed viable, a cesarean section was done by Dr. Van Dolsen, and he delivered a living male child that died shortly after delivery. At the time of operation, the cervix was palpated vaginally and found to be hard and rigid but not involved by the carcinomatous mass. Following the operation, the patient's course was progressively downhill, with marked emaciation, an irregular temperature ranging between 100 and 103 F, rapid pulse, increasing anemia and a progressively increasing leukocytosis, the total leukocyte count just prior to death being 94,500 with 98 per cent polymorphonuclears. On Jan 30 1929, an enlarged right inguinal gland was removed. On histologic examination it showed metastatic squamous cell carcinoma, the section presenting numerous epithelial pearls. On Feb 3 1929, a rectovaginal fistula developed, the

condition grew worse and the patient died, Feb 9, 1929. Permission for an autopsy unfortunately could not be obtained. Vaginal examination at the time of death showed the presence of the rectovaginal fistula, the tumor was felt as a flat infiltration of the remaining posterior vaginal wall. The cervix was apparently still free. A small portion of the tumor was removed from the rectum posteriorly for section. Histologically it showed invasion of the rectal wall down to the mucosa by tumor cells.

COMMENT

Primary squamous cell or epidermoid carcinoma of the vagina is a comparatively rare condition, making up about 0.43 per cent of all carcinomas of women and from 0.26 to 3 per cent of carcinomas involving the female reproductive organs. Among the possible exciting factors, the irritation caused by pessaries receives frequent mention in the literature, but as Williams¹ pointed out, the irritation theory is not strongly supported, since the vagina is more subject to all kinds of irritation than other organs, moreover, vaginal prolapse and invagination conditions of maximum irritation, are seldom accompanied by cancer. The proportion of cases secondary to the use of the pessary is extremely small in comparison to the enormous number of instances in which the pessary is used. Certainly, in the case just described, this factor could be excluded. Several cases have been reported of carcinoma developing on the site of epithelial hyperplasias, such as leukoplakia, ichthyosis or kraurosis, but these conditions usually occur in women of advanced years.

Embryologically, the vagina is derived from the lower end of the wolffian ducts, the cells of which are of epiblastic derivation. It is possible that during the process of development of papillary structures like the vaginal mucosa, some epidermoid cells may become detached and form rests from which carcinoma may develop. If one assumes that these rests exist, the possibility then suggests itself that in the case in question the marked proliferation of tissue accompanying pregnancy might have served as a stimulus to such epithelial rests and thus predisposed them to the formation of cancer. The exact influence of pregnancy as an exciting factor in the production of cancer is not known, conflicting opinions exist, but the majority favor the idea that, once established carcinomatous lesions seem to grow more rapidly with the advent or in the presence of pregnancy, possibly because of the increased nutrition and vascularization of the tissues. Search of the literature failed to find any information or data concerning the influence of pregnancy in the production of carcinoma, provided, of course, that the soil is fertile.

The onset of the vaginal bleeding, which was the first symptom the patient complained of, occurred late in the fifth month of pregnancy.

1 Williams. New York M. Rec. 60:841, 1901.

and death occurred in less than three months from this time. It seems hardly likely that the tumor could have been present for more than five months without giving rise to any symptoms, and one can assume, therefore, that the tumor must have grown after the onset of pregnancy rather than before it.

The course of these tumors is usually rapid, the shortest time from the onset of the initial symptoms in Williams' series being eight months, the longest twenty-six and five-tenths months and the average sixteen and five-tenths months. The total duration of the disease from the time of the initial symptoms in this patient was less than three months, it is not unlikely, however, that the operative procedure served to shorten the patient's life materially.

Another unusual feature in this case was the age of the patient, she being unusually young not only for carcinomatous tumors in general, but particularly for carcinoma of the vagina. The usual age for this tumor, according to Williams' statistics, is that between 50 and 60 years which is a little older than that for carcinoma of the cervix. Williams' youngest patient was 17 years old, he regarded reputed examples of vaginal cancer occurring at earlier ages with suspicion, this applied especially to the oft-cited cases in a child aged $3\frac{1}{2}$ and in a girl aged 9, described by Guesant and by Johannowsky, respectively, in which the disease was evidently sarcomatous.

Although the tumor is seldom seen in its early stages, according to Pozzi² it occurs initially in one of two forms—either as a papillary growth in the form of single or multiple warts or as a nodular or infiltrative form. In the more advanced stage, cauliflower, villous, highly vascular and more frequently ulcerative types are seen. The usual location is on the posterior vaginal wall, most frequently in its upper segment. From here the disease usually spreads backward to the rectum with symptoms of obstruction and eventual formation of a rectovaginal fistula, as occurred in this case. Spread of the disease to the adjacent lymph glands of the ilio pelvic group and particularly both inguinal groups is usually a late manifestation. Dissemination to the internal organs or distant parts is uncommon, death usually occurring before this from either progressive cachexia or, not uncommonly, peritonitis.

Histologically, the tumor presents the usual features of squamous cell carcinoma, except that pearl formation and cornification are not prominent.

SUMMARY

A case of primary squamous cell carcinoma of the vagina, an uncommon type of tumor, is reported as a rather unusual complication of late

² Pozzi. Quoted by H. S. Crossen. *Diseases of Women*, ed. 5, St. Louis 1922, p. 314.

pregnancy in a girl of 16. The onset of the vaginal bleeding, which was the initial symptom, occurred late in the fifth month of pregnancy, making it likely that the formation of a tumor occurred after the onset of the pregnancy, rather than before it. Because of the extreme youth of the patient, the predisposing factors usually mentioned, namely, pessaries and epithelial hyperplasia such as kraurosis, can be excluded. It is therefore suggested that the origin of the tumor might have been in epithelial rests of the wolffian ducts, these rests being stimulated to the production of cancer by the proliferative changes of early pregnancy. The course of the disease in this case was much shorter than in any of the previously reported cases, death from marked cachexia occurring in less than three months from the time of the appearance of the initial symptom.

I EXPERIMENTALLY INDUCED LOCALIZED INFLAMMATORY REACTIONS IN THE LIVER*

GEORGE M HIGGINS, PH D

AND

GEORGE T MURPHY, MD

ROCHESTER, MINN

From the histophysiologic point of view, Maximow¹ arranged the connective tissue and the blood of vertebrates into three vast groups (1) fixed, highly differentiated cells which produce the fibrous inter-cellular substance in connective tissue, known as fibrocytes, (2) fixed or free cells which possess marked ability for phagocytosis and are especially prominent in the liver, spleen, lymph nodes and bone-marrow and (3) hemocytes, which include all circulating elements in the lymph and blood stream. As early as 1902, Maximow² recognized three principal cell types in any field of inflammation. These are (1) fibroblasts, or the common connective tissue cells, (2) polymorphonuclear leukocytes, and (3) the mononuclear exudate cells, or polyblasts as he called them, perhaps the most important in any inflammatory reaction of defense. The origin of these three types of cells and their ontogenetic relationships is a problem concerning which the opinions of leading cytologists are still greatly at variance.

It is not our purpose to review the extensive literature covering the details of the experimental data that are available. The reader is referred to the articles of Maximow and Bloom³ for full bibliographies and complete interpretation. Our interest in the problem was not immediately related to the relative potency of the connective tissue cell or to the origin of the various kinds of cells which appear in any generalized inflammation. But since the Kupffer cell of the liver is a mesenchymal cell, placed in group 2 of Maximow's classification, we were interested to know the extent to which these cells would react in the restoration of aseptically induced hepatic lesions. The reaction of the stellate cells in the liver to a bacterial invasion has been studied

* Submitted for publication, Jan 4, 1929

* From the Division of Experimental Surgery and Pathology, the Mayo Foundation

1 Maximow, A A Morphology of the Mesenchymal Reactions, Arch Path 4 557 (Oct) 1927

2 Maximow, A A Experimentelle Untersuchungen uber die entzündliche Neubildung von Bindegewebe, Jena, Gustav Fischer, 1902, vol 7, p 262

3 Bloom, William The Origin and Nature of the Monocyte, Folia haemat 37 1, 1928

as well as the response induced by the introduction of foreign bodies into the hepatic parenchyma. Bloom⁴ reported observations on the Kupffer cells in a study of abscesses induced by infection with *Bacterium monocytogenes*, whereas Biebl⁵ reported his observations on the reaction of the reticulo-endothelial cells in the liver to foreign bodies in the form of autogenous transplants, such as kidney and muscle.

The Kupffer cells of the liver are a part of the system of fixed histiocytes which are localized in various parts of the body, they are identified and grouped, to a large extent, by their behavior toward vital dyes. Kupffer cells react to supravital staining with neutral red in the same way as wandering cells of common connective tissue, and, in tuberculous lesions of the liver, they have been shown to hypertrophy, proliferate mitotically and become free histiocytes in the blood stream. They may form epithelioid cells, and it is not uncommon to see in vital staining in rabbits the fusion of such free epithelial cells into giant cells. All cells lining the hepatic sinusoid are not actively phagocytic at any one time. Following one or two injections of a suspension of graphite or of any one of the vital dyes, a few Kupffer cells may always be seen literally packed with granules and projecting far into the lumen of a sinusoid, while others, apparently inactive, lie closely applied to the parenchymal cell. Following repeated injections, however, many of these hitherto resting phagocytes become active but even in the face of prolonged vital staining, one invariably sees a few quiescent histiocytes lying along the parenchyma, without evidence of phagocytosis. It has been stated that these cells, following extensive phagocytosis, desquamate, enter the blood stream as blood histiocytes and are filtered off in the lung. However, we have identified Kupffer cells with particles of graphite in hepatic lobules of rabbits, six to eight months following intravenous injection. The origin of these stellate cells in the sinusoid is uncertain. They probably do not arise from common vascular endothelium, the presence of which, within the hepatic lobule, may rightly be questioned. Should they arise in situ we would expect to encounter mitotic figures more frequently than we do. Elliott⁶ suggested that these histiocytes of the reticulo-endothelial system, lining vascular sinusoids, may be blood monocytes which adhere to the walls and remain temporarily fixed. This conclusion is open to question, and yet there are many experimental data to lend it credence.

4 Bloom, William. The Formation of Abscesses in an Infection with *Bacterium Monocytogenes*, Arch Path 6 995 (Dec) 1928.

5 Biebl, Max. Eine experimentelle Bindegewebstudie am Reticuloendothel der Leber, Deutsche Ztschr f Chir 218 306, 1929.

6 Elliot, Caliste. The Origin of the Phagocytic Cells in the Rabbit, Bull Johns Hopkins Hosp 39 149, 1926.

De Haan and Hoekstra,⁷ in a series of ingenious experiments concluded that the Kupffer system in the liver is not stable but that it is constantly changing in the number of its components. They directly identified the Kupffer cell with the clasmatocyte. After developing large numbers of mononuclear cells in the peritoneal cavity of rabbits by injecting large quantities of a solution of sodium chloride, they marked the cells so that subsequently they could be identified by injecting trypan blue. These large mononuclear cells which contained granules of trypan blue were then injected into the portal stream of another rabbit. Sections of the liver of the second rabbit contained typical Kupffer cells with the granules of trypan blue within them, although the spleen and the lung did not contain any of the injected cells. The authors concluded that the injected mononuclear cells had been intercepted by the liver and had transformed into functional Kupffer cells. They observed all transitions from the free spherical mononuclear cell which they introduced to the fixed oval or elongated cell closely applied to the hepatic trabecula.

The relation of the Kupffer cells of the liver to the cells of the blood stream was recently rather unduly emphasized by Malyschew⁸ who ascribed to them a widely diversified potentiality. In aseptic lesions of the liver according to this author these cells may hypertrophy, reorganize and differentiate into promyelocytes, myelocytes, megakaryocytes, monocytes and fibroblasts and they may even proliferate and regenerate vascular capillaries. In fact from these observations one might well conclude that the Kupffer cell could serve as a stem cell from which all other hemocytes could arise. Siegmund-Koln⁹ in studies following the injection of living colon bacilli into the portal vein, also concluded that the Kupffer cells after desquamating gave rise to polymorphonuclear leukocytes, conclusions which since have been proved false.

Bungeler and Wald¹⁰ in studies on inflammatory lesions were unable to substantiate Malyschew's conclusions. These authors regarded the stellate cell as a highly differentiated cell which may give rise to monocytes but never transforms into polymorphonuclear leukocytes.

7 De Haan J. and Hoekstra R. A. *Ersuche über die Herkunft und die Deutung des Kupfferschen Systems der Leber*. Arch. f. exper. Zellforsch. **5**: 35, 1927.

8 Malyschew B. *Ueber die Rolle der Kupfferschen Zellen bei aseptischer Entzündung der Leber*. Beitr. z. path. Anat. u. z. allg. Path. **78**: 1, 1927.

9 Siegmund-Koln. *Untersuchungen über Immunität und Entzündung*. Verhandl. d. deutsch. path. Gesellsch. **19**: 114, 1923.

10 Bungeler W. and Wald. *Beiträge zur Herkunft der polymorphkernigen Leukocyten. Die Bedeutung der Kupfferschen Sternzellen bei der Entzündung*. Virchows Arch. f. path. Anat. **270**: 150, 1928-1929.

Whereas Schilling¹¹ in reported observations of cases of monocytic leukemia described the transformation of Kupffer cells into monocytes, Bloom,⁴ in studies on experimental abscesses in the liver, could not recognize any participation by these stellate cells in the marked production of mononuclear exudative phagocytes. Bloom regarded these exudative mononuclear cells of a hematogenous source as being of lymphocytic or monocytic origin. Biebl, in studies on the reaction of the reticulo-endothelial cells of the liver to autogenous transplants, attributed the mononuclear reaction that ensues to proliferation of the polyblasts of the periportal spaces and the Kupffer cells of the sinusoids.

MATERIAL AND METHODS OF STUDY

In order to determine the reaction of any given cell to a foreign stimulus, it is essential that it be marked in some way to identify it among other cells with perhaps equal potency. Accordingly, in this study the injection method was employed to delineate the phagocytic cells of the liver, prior to inducing the aseptic lesion. A suspension of graphite frequently employed in our laboratory for intra vitam studies was injected intravenously into an animal from two to three days before the operative procedure. Into some animals only small amounts, 2 or 3 cc for each kilogram of body weight, were injected, into others, larger amounts, sometimes as high as 25 cc for each kilogram of body weight, were injected. In this way, the reaction of a liver in which the phagocytic cells were only lightly speckled with graphite could be followed, as well as if the cytoplasmic bodies were completely distended. Within a short time following these injections, laparotomy was performed under ether anesthesia, and a hot instrument, 2 mm in diameter, was introduced into the hepatic substance. From three to four such puncture wounds were made in the liver thus exposed. At intervals following the operative procedure, the animals were killed, the blocks of hepatic tissue containing the sites of injury were removed, fixed in Zenker-formaldehyde solution and stained with hematoxylin and eosin, van Gieson's stain, and Mallory's connective tissue stain. Studies were made at one hour, three hours, six hours, ten hours, twenty-four hours, forty-eight hours, seventy-two hours, one week, two weeks, three weeks and one month following the production of the aseptic lesion in the vitally stained liver. Rats, rabbits and dogs were used, and although the results attained were essentially identical in these animals, this report will be restricted to the reactions encountered in the liver of the albino rat.

EXPERIMENTAL OBSERVATIONS

Kupffer Cells in Normal Liver.—Following the injection of the preparation of graphite and prior to the operation, sections of the liver showed that the injected material had been taken up by the Kupffer cells which line the hepatic sinusoids and that most of these phagocytic cells contained graphite in varying amounts (fig 1). Many of them, however, had been inactive and could be identified along the walls of sinusoids in their resting condition. The graphite-laden cells varied in size. Their elongated processes might frequently extend over two or three hepatic cells, and often small pseudopodial processes reached into intervals between adjacent hepatic cells. Occasionally, well laden cells fixed at places

11 Schilling, Viktor. Der Monozyte in trialistischer Auffassung und seine Bedeutung im Krankheitsbilde, *Med Klin* 1 563, 1926.

to the sinusoidal wall projected into the lumen of the sinusoid, and in some instances the processes appeared to have been retracted, the cell was spherical presenting every evidence of a mononuclear cell free in the blood stream. Occasionally, from forty-eight to seventy-two hours after injection, graphite-bearing cells appeared in the interlobular tissue surrounding the blood vessels and the bile ducts. These cells resembled, both in size and staining reaction the mononuclear cells so often encountered free in the lumen of the sinusoid, and their presence within the periportal tissue might be due to a migration from the site

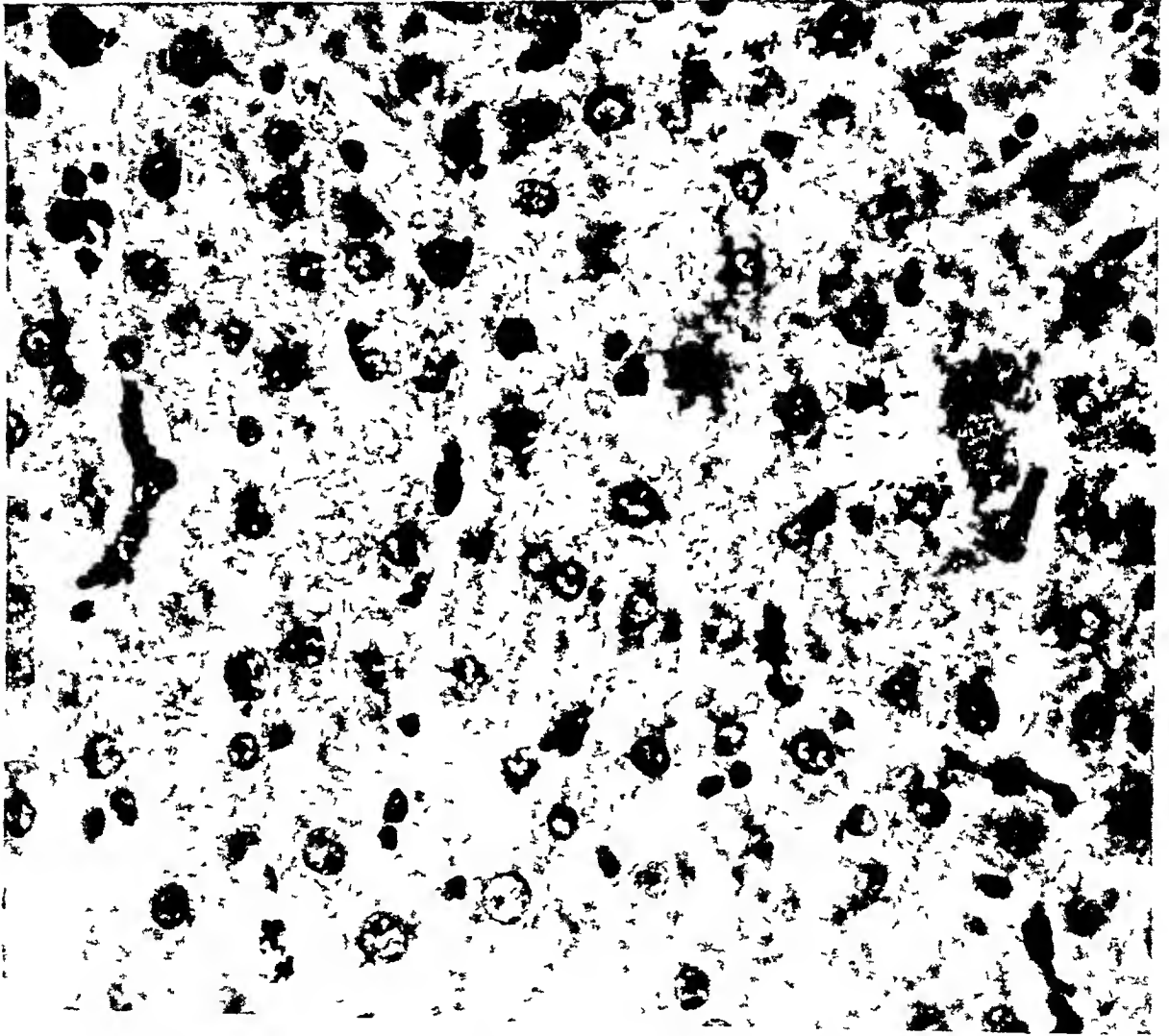


Fig. 1—Normal rat's liver after an injection of graphite prior to injury ($\times 300$)

of origin within the lobule, or the blood stream, to the mesenchymal cells surrounding the interlobular vessels. The relation of the stellate cells to these mesenchymal cells of the periportal spaces, which proliferated so abundantly following the production of the lesions, will be considered more in detail elsewhere in the paper.

Kupffer Cells in Injured Liver One Hour After Injury—One hour after the injury to the hepatic substance with a hot needle, marked congestion extended throughout the injured region. A prominent zone of congested hepatic substance

separated the inflamed region from the normal hepatic tissue surrounding it. The hepatic cells throughout the site of the lesion were necrosed and spindle-shaped and contained oval, elongated nuclei. Kupffer cells within the region were destroyed, and scattered granules of graphite abounded throughout. Polymorphonuclear infiltration had not yet taken place.

Hepatic tissue peripheral to the lesion was not essentially unlike that prior to operation. The hepatic sinusoids were not as yet congested, but the phagocytic cells, for a considerable distance peripheral to the lesion, were no longer stellate.

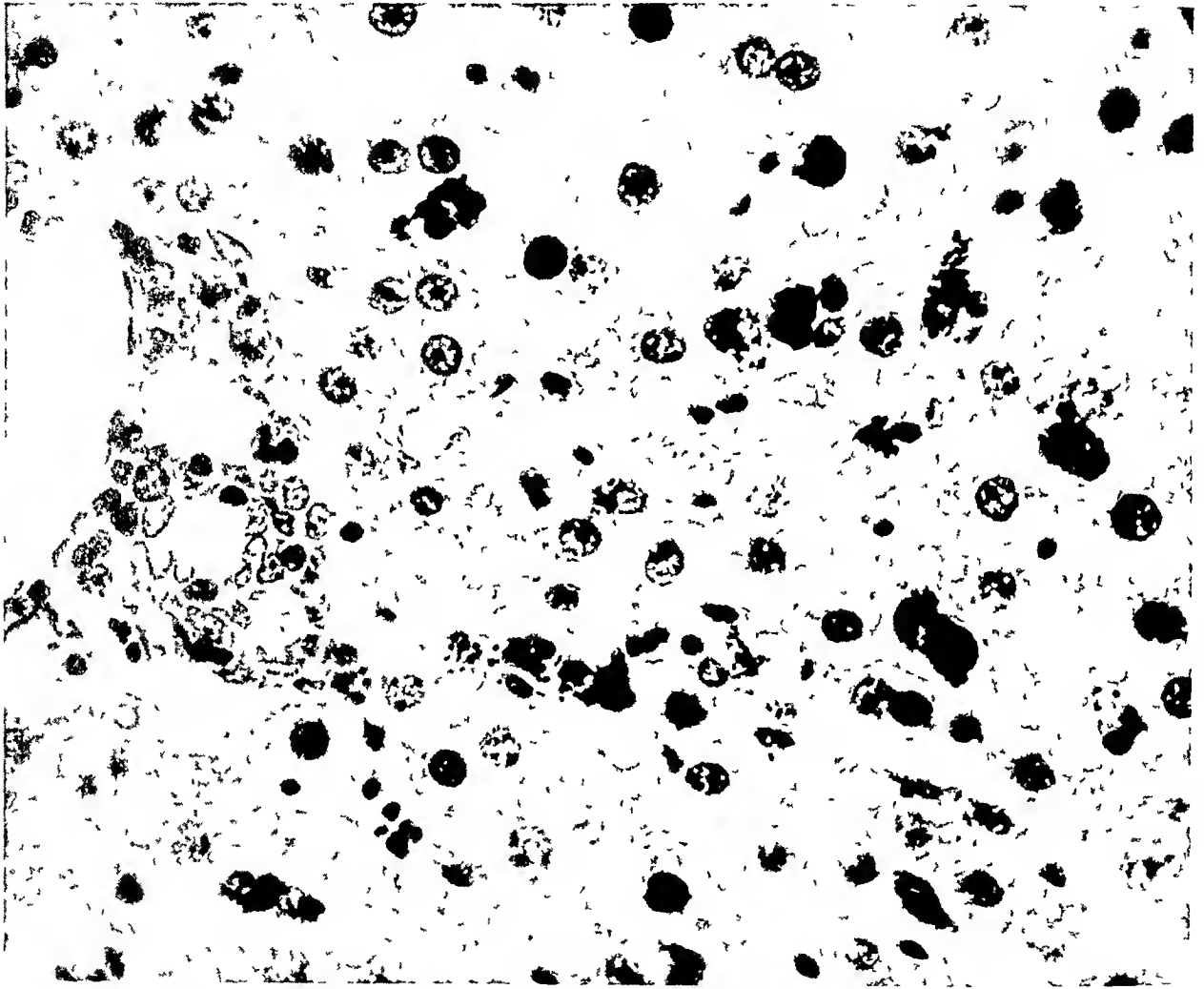


Fig 2—Hepatic parenchyma, adjacent to site of injury, one hour after operation ($\times 300$)

Their processes had been retracted, the cells were more spherical, many lay free within the lumen, and there was some evidence that migration of these cells had begun (fig 2). This pertains equally to those Kupffer cells of the sinusoid which did not contain graphite. They, likewise, were swollen, lay frequently free in the lumen, and showed evidences of migration, either toward the lesion, or, more commonly, toward the interlobular connective tissue spaces. Hyperactivity of these regions as centers or foci for cellular proliferation, so extensive in the later repair of the lesion, was not manifest as yet.

Six Hours—Six hours after the injury, the cytoplasmic bodies of the necrotic cells were largely disintegrated, and the nuclei, for the most part, had disappeared. A few polymorphonuclear leukocytes extended throughout the lesion, and large numbers of mononuclear graphite-laden cells abounded throughout the perinecrotic tissue. Many of these lay free in the sinusoids, others appeared to lie between hepatic cells within trabeculae, many others lay among the mononuclear cells now proliferating from the mesenchymal cells in the perilobular spaces. This cellular proliferation in the portal spaces was characteristic, but mitotic figures were exceedingly rare, and one wonders whether amitotic cellular division may not be the rule. Binucleate cells often were encountered, and elongated shapes were such as often to suggest amitosis.

Twenty-Four Hours—Twenty-four hours after injury, the organization of the lesion was well advanced. In the center of the necrotic region was a fibrinous, bloody exudate containing many polymorphonuclear leukocytes and a few monocytes. These cells had phagocytosed many of the granules of graphite which had been scattered throughout the site of the lesion at the time of injury. Throughout portions of the necrotic region toward the periphery, there were numerous foci, or centers, in which the neutrophilic granulocytes were exceedingly abundant, whereas, at the periphery of the necrosed region, adjoining the normal parenchyma, small nests of mononuclear cells had accumulated. Many of these mononuclear cells contained graphite, many did not. Marked congestion characterized the uninjured adjacent hepatic parenchyma. The sinusoids were wide open, and the Kupffer cells which yet remained attached projected far into the lumen. The whole field differed essentially from that of a liver into which graphite had been injected, prior to the operation. Pigmented cells were not evenly distributed, but were more concentrated, especially in the interlobular spaces around the bile ducts and blood vessels, centers which acted as prominent foci for the proliferation of large numbers of mononuclear cells.

Forty-Eight Hours—The center of the necrotic region, at forty-eight hours after injury to the liver, was largely cleared of free graphite and cellular fragments, owing essentially to the phagocytic activity of both the granulocytes and the agranulocytes. At this time, most of the granulocytes were massed into a wide circular band extending throughout a region midway to the periphery of the necrotic region, ingesting free graphite and fragmented hepatic cells. At the periphery, but within the necrotic region adjacent to the normal parenchyma, many mononuclear cells, both with and without graphite, largely ameboid, contributed toward the formation of a delineating wall (accentuated in later stages) which separated the necrotic from the normal tissue. Graphite-laden cells in the hepatic parenchyma were less frequent, and many appeared to be migrating through hepatic trabeculae, either toward periportal spaces or directly to the lesion.

Seventy-Two Hours—The reaction at the site of injury in a rat's liver, seventy-two hours after operation, differed only slightly from that at forty-eight hours. The region of fibrinous exudate was larger and the circular zone of granulocytes was replaced by a group of active granulocytic centers (fig 3). The deposition of mononuclear cells around the necrotic region, delineating it from hepatic parenchyma, was more extensive, so that a wall, from four to five cells thick, was formed. Granulocytes were absent from this peripheral zone of mononuclear cells. Most of the cells forming this zone contained graphite, a few did not, and it appeared to us that these cells had migrated to the site of injury from the surrounding hepatic parenchyma. Many of these mononuclear cells, relatively spherical in earlier stages, were largely spindle-shaped and elong-

ated cytoplasmic processes with collagenous intracellular material extended out from ovoid, centrally placed nuclei for considerable distances, forming connective tissue cells with fibrous processes. Most of these elongated cells contained very small particles of graphite which might be identified out in the finer protoplasmic extensions, and many did not, thus it appeared to us that the extensive capsule of fibrous tissue, identified in later stages, had its inception at this stage, arising from mononuclear cells which had migrated from the hepatic sinusoid and from the local histiocytes of the perlobular spaces to the site of injury. If proper



Fig 3—Organization of entire lesion and adjacent parenchyma at seventy-two hours after operation ($\times 48$)

sections were secured, one often identified a "streaming" movement of these mononuclear cells from the periportal regions, along the perivascular spaces in the interlobular regions to the site of the lesion. Littoral cells of the sinusoid probably did not migrate for any distance in the lumen toward the inflamed area, but we were inclined to believe that there was a migration free from the sinusoid, directly through parenchymal tissue, to adjacent perivascular mesenchyme, and thence these cells, together with polyblasts which were proliferated from parent histiocytes around the blood vessels, migrated toward the site of inflammation.

Five Days—A microscopic section of an inflammatory lesion and its surrounding hepatic parenchyma five days after operation revealed two essential contrasts with that of a like lesion of seventy-two days' duration. Most apparent, perhaps, was the reduction in graphite-laden cells throughout the hepatic substance peripheral to the lesion. Scattered, pigmented cells abounded in the five-day stage, but these were appreciably less in the hepatic parenchyma at this time and suggested a breaking away, or a migration, of those cells which had so extensively phagocytosed the injected particles of graphite. In further contrast with the

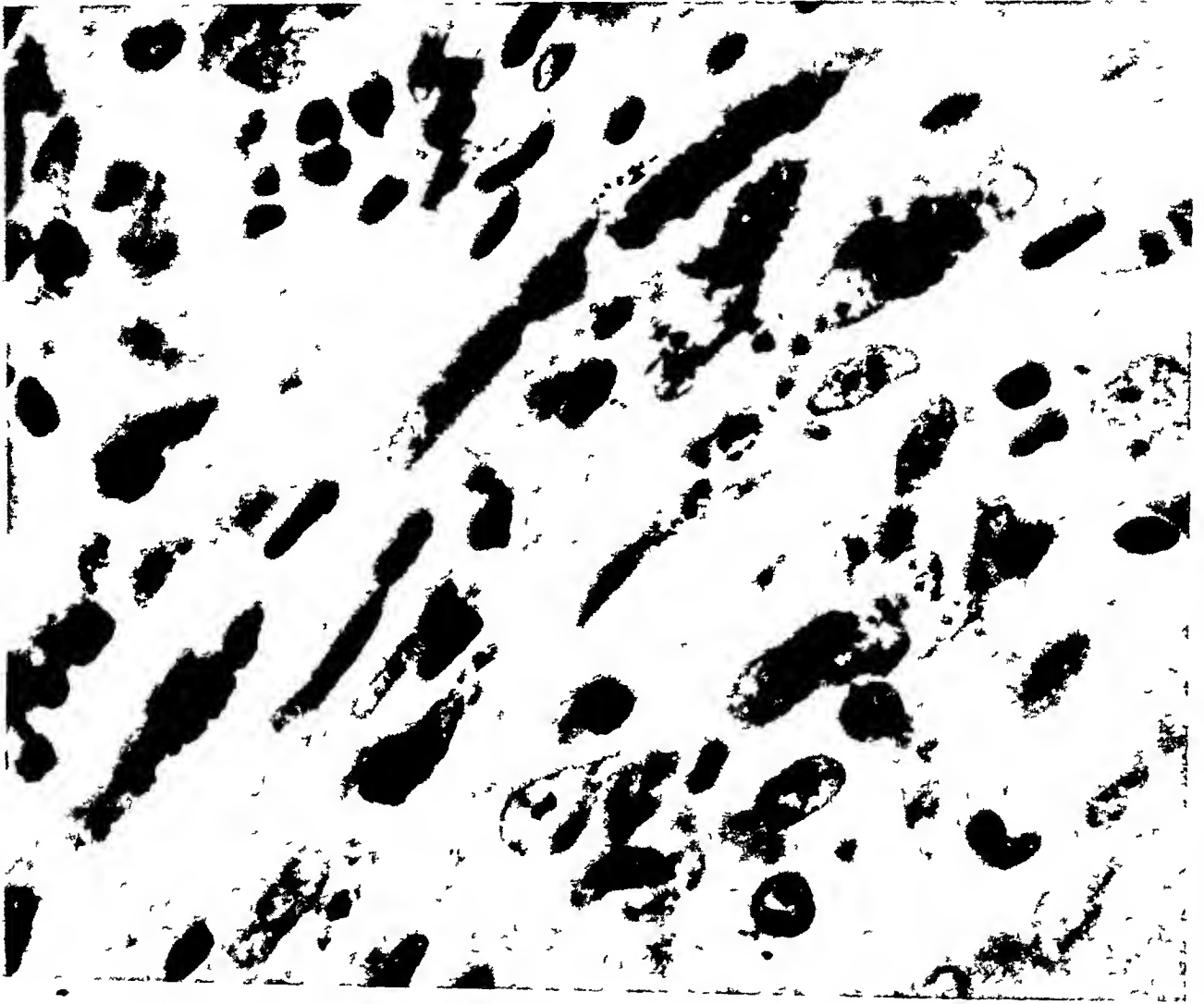


Fig 4—Portion of capsule, surrounding lesion, six days after operation, elongated, spindle-shaped, graphite-laden cells are seen ($\times 1400$)

earlier, seventy-two hour stage, the wall of limiting capsule surrounding the lesion stood out in marked contrast with both the acidophilic, necrosed hepatic tissue and with the more darkly stained, normal parenchyma. The size of the wall had increased to a layer from ten to twelve cells thick, all cells of the mononuclear series, but more striking, perhaps, was the large accumulation of particles of graphite which were gathered into the cells which comprised this wall. Many of these mononuclear cells were fibroblast-like spindle-shaped, with long, fibrous processes (fig 4), whereas others were more spherical still, with

amoeboid characteristics. There were no centers of granulocytic activity, and such neutrophilic leukocytes as did abound were distributed somewhat generally throughout the necrotic area, but they never were encountered in the capsule of the lesion. Mononuclear cells, however, occurred within the necrosed parenchyma probably moving in somewhat from the capsule as well as arising in situ from mononuclear cells of the blood or from local histiocytes not destroyed at the time of injury.

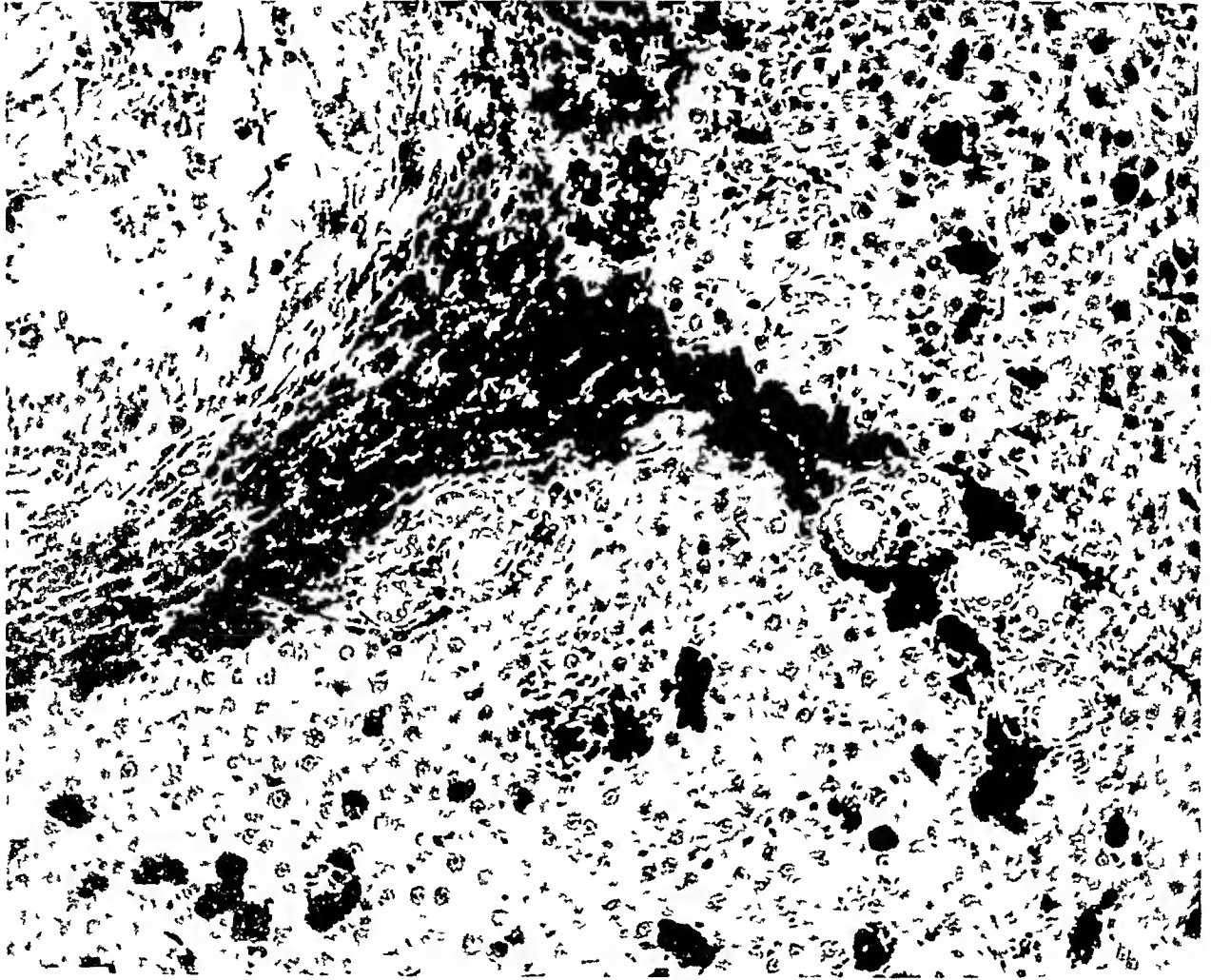


Fig 5—Portion of capsule surrounding lesion twenty-one days after operation in a rat which had received a heavy injection of graphite ($\times 200$)

Mesenchymal Cell Proliferation in Liver—Cellular proliferation from the local mesenchymal cells of the periportal spaces appeared to be of a rhythmic nature. Proliferation of these cells was marked during the earlier phases of the cellular response to the injury, and again, two weeks after injury, zones of mononuclear cells, many times normal proportions, surrounded the interlobular bile ducts and blood vessels. Mitosis in these zones was not common, and yet occasional mitotic figures were encountered. Whereas one might hesitate to ascribe these marked increases in numbers of cells to amitosis, yet the elongated shape of the nuclei so often encountered was most suggestive. Two types of

mononuclear cells characterized these proliferative zones. There were small, darkly stained basophilic cells with compact chromatin and larger cells, with lightly stained nuclei and a loosely arranged network of chromatin. Scattered throughout these zones were many graphite-laden cells, for the most part of the larger type, which seemed, to a large extent at least, to have migrated to these centers from the closely adjacent sinusoid. The majority of the cells in these zones, however, were without graphite, and, we felt had arisen *in situ* from the local histiocytes which abounded in the normal liver and from lymphocytes which, no doubt, had migrated from the hepatic sinusoids and blood vessels to these centers, changing into monocytes and into tissue histiocytes. Typical blood monocytes were not abundant in these proliferative zones, and yet one might identify a sufficient number of intermediate forms to indicate that, in accordance with Bloom's¹² (1927) conclusion, monocytes arise by transformation of the smaller lymphocytes. Furthermore, it was impossible to determine whether these polyblasts were of hematogenous or histiocytic origin.

In rats that had received rather heavy injections and the livers of which had been studied at two and three weeks following injury, the migration of these graphite-laden mononuclear cells to the inflamed region had been so extensive that a complete, heavily infiltrated wall entirely delineated the site of injury from the surrounding hepatic parenchyma. This reaction was so pronounced that in some instances so effective a barrier had been produced as to form a black wall around the region of necrosis (fig 5). Furthermore, the migration of graphite-laden cells from the peripheral parenchyma to this wall was frequently so extensive as to form, in histologic section, heavily infiltrated paths leading toward the necrotic region as a center (fig 5). These paths, along which mononuclear cells passed to the lesion, frequently extended from the peripheral parenchyma widely remote from the lesion.

COMMENT

Supravital technic or other refined methods designed to differentiate cells types have not been employed in this study, and accordingly definite proofs of cellular lineage have not been presented. We wished rather to know whether the phagocytic cells of the liver, recognized mesenchymal cells, could well function in the organization of aseptically induced hepatic inflammatory lesions.

The injection method as a means for the identification of cells is a fairly satisfactory one. To be sure, reticulo-endothelial elements throughout the body phagocytose injected materials as effectively as do those within the liver, so that phagocytic cells in the spleen or bone-marrow, for example, are labeled in a manner similar to those in the liver. It is not likely, however, that these fixed histiocytes, which may or may not become free cells from time to time, will essentially modify a slight inflammatory reaction within the liver. Circulating lymphocytes and monocytes have been shown to be sharply differentiated from these histiocytes, and although under conditions of pathologic stress monocytes

¹² Bloom, William. Transformation of Lymphocytes of Thoracic Duct into Polyblasts (Macrophages) in Tissue Culture, *Proc Soc Exper Biol & Med* 24:567 1926-1927.

may transform into histiocytes and fibroblasts, their origin is essentially divergent. Accordingly, we felt that by marking the stellate cells of the liver by their ability to engulf foreign bodies, we could well follow their activity and feel reasonably sure that we were dealing with the cell that was the original phagocyte in the liver and not cells of the lymphoid group.

Accordingly, with this consideration of the method, intravenous injections of a preparation of graphite were made in a large series of rats, so that at least a majority of the Kupfer cells contained varying amounts of the black pigment. Slight puncture wounds were then made in the hepatic substance, under aseptic conditions, and the cellular reactions were studied for a period of one month thereafter.

Cappell¹³ stated that removal from the blood stream of various materials by the liver is due chiefly to the endothelium and stellate cells of the sinusoids. It is questionable whether hepatic sinusoids are lined with regular endothelium. Occasional, flattened, endothelial-like cells lie along the hepatic parenchyma, and we have in the past, no doubt, identified these cells as parts of an hepatic endothelium. Even with special staining methods, however, such as the Rio Hortega or the Bielschowsky, we have not been able to identify a continuous cytoplasmic structure along the margin of the sinusoid and we feel that the hepatic parenchyma is separated from the blood stream by an incomplete partition consisting of a reticulum by means of which the Kupfer cells of the liver are held to the parenchyma of the liver.

Following injection of a suspension of graphite, about 3 cc. in a rat weighing 175 Gm. the blood stream was cleared within a few minutes, and the particles were found adherent to the cells lining the hepatic sinusoids. Within a few hours phagocytosis had taken place, the fine granules of graphite had been taken up and had now accumulated into the "segregation apparatus" within the cytoplasm of these cells. Particles of graphite were never identified in the local histiocytes of the periportal spaces immediately following an injection, and we do not believe that free graphite, under the conditions of our experiment, ever migrated through hepatic parenchyma to the periportal spaces.

In studies on the endothelium in the production of polyblasts in inflammation, Lang¹⁴ concluded that carbon particles may enter endothelial cells, not as a result of phagocytosis, but more as a result of physical properties associated with surface tension. He concluded that particles of carbon merely pass through endothelium and are then taken

13 Cappell, D. F. Intravital and Supravital Staining, *J. Path. & Bacteriol.* **32**: 595, 1929.

14 Lang, F. J. Rôle of Endothelium in the Production of Polyblasts (Mononuclear Wandering Cells) in Inflammation, *Arch. Path.* **1**: 41 (Jan.) 1926.

up by cells surrounding the capillary wall. It is possible that the presence of graphite-laden cells in the periportal spaces of our experimental rats is explained in that way, namely, that particles had forced their way through the endothelium of the interlobular capillaries and had been engulfed by the polyblasts surrounding them. We have never seen particles of graphite in these endothelial cells, however, and the fact that the number of graphite-laden cells in the periportal spaces was so much greater in the later stages, long after the blood stream had been freed of floating particles, leads us to conclude that the majority of these graphite-laden cells had migrated from the blood stream and the sinusoids.

The inflammatory lesions were induced in the livers of these rats soon after injection, thus, in most cases, they were induced prior to the migration of the phagocytic cells into the periportal spaces. Within a few hours, however, following the injury to the parenchyma of the liver, the Kupffer cells in the sinusoids around the site of the lesion became swollen, projected far into the lumen and retracted their cytoplasmic processes. At this time, large mononuclear cells lay free in the blood stream, and, since these cells presented a staining reaction and a distribution of graphite identical with that of the attached phagocytic cells, one may conclude that these cells in the lumen were desquamated Kupffer cells. This observation, of course, has been made frequently by other workers.

During this initial response by the Kupffer cells of the normal parenchyma, slight changes took place within the inflamed region. The necrosed hepatic cells were greatly swollen, they rapidly disintegrated, and particles of graphite, contained within phagocytic cells prior to operation, were scattered throughout the lesion. Granulocytes did not appear for six or eight hours, but in the twenty-four hour lesion they were abundantly scattered throughout the more central portion of the necrosed parenchyma, engulfing exudate and graphite residue. Mononuclear cells were few within the center of the lesion, although at the periphery, along the line of transition from necrotic to normal parenchyma, many such cells abounded. These mononuclear cells, we felt, were local histiocytes which were within the zone of hepatic parenchyma immediately surrounding the lesion.

Within twenty-four hours after the operation, proliferation of the local histiocytes or polyblasts within the periportal spaces had taken place, so that a large number of small mononuclear cells surrounded the blood vessels and the bile ducts. Interspersed among these were numbers of cells which contained the graphite much as did the free cells in the sinusoids and the stellate cells still attached. These graphite-laden cells of the portal spaces, we believe had migrated either directly

through hepatic parenchyma or from the blood stream to these regions. The finding of occasional mononuclear cells, containing graphite within the hepatic trabeculae, forces the opinion that an actual migration between adjacent hepatic cells of a trabecula may take place. Although many graphite-laden cells abounded in the portal spaces, many such cells still remained in the adjacent sinusoids and many phagocytes were as yet fixed to their original position, so that all Kupffer cells did not immediately desquamate. All mononuclear cells within the sinusoids, fixed or free, did not contain graphite. In fact, many did not, but we were unable to determine whether these Kupffer cells, apparently new in the field, had arisen as a proliferation of previously existing cells, or whether, as de Haan and Hoekstra thought they had migrated to this position.

The further cellular reaction to the inflammatory lesion consisted in but an elaboration of the processes already initiated. The infiltration of polymorphonuclear neutrophils became exceedingly marked, especially within the central portions of the lesion where phagocytosis of cell fragments and particles of graphite rapidly occurred. Granulocytes were rare in the peripheral fourth of the circular lesion, a zone in which the mononuclear exudate cell was most active. Lesions at forty-eight hours and seventy-two hours after operation showed a heavy infiltration of such cells, sufficient to form a wall from 6 to 10 cells thick. Many of these cells contained graphite, many did not, and we believe that they had appeared there, coming partly from preexisting mononuclear cells, but largely from cells which had proliferated from the local histiocytes of portal spaces and wandering phagocytes from hepatic sinusoids. Our evidence for this lies essentially in the frequent identification of the "streaming phenomenon" in which cells, both with and without graphite, appeared to be migrating in mass formation toward the lesion. We do not presuppose that the presence of graphite within these mononuclear cells at the inflammatory site indicates in every case, direct lineage to the phagocytic cell of the sinusoid, for the residual graphite free within the lesion at the time of operation was no doubt ingested by the mononuclear cells in situ. However, we do feel that many of the graphite-laden mononuclear cells traversing the trabeculae, or migrating together with the proliferating local histiocytes toward the lesion, there to contribute toward its encapsulation, were, to a large extent, directly related to the Kupffer cells of the sinusoid. In his studies on the cellular reaction toward the transplantation of foreign tissues into the hepatic parenchyma, Biebl observed this same sort of reaction that we have encountered in inflammatory lesions, namely, marked proliferation of the local connective tissue cells and migration, together with many Kupffer elements, toward the site of the transplant.

This inflammatory reaction within the liver was not unlike that which arises in lesions elsewhere in the body. The granulocytic reaction, occurring within from twenty-four to forty-eight hours following injury, appeared to be entirely independent of the mononuclear infiltration. There was no evidence to support the contention of Malyschew that the polymorphonuclear leukocyte arose from the Kupffer cell or other monocyte. The polymorphonuclear reaction was essentially restricted to the more central portion of the lesion and was apparently related in origin to comparable cells of the blood stream. These cells appeared within the lesion, engulfed foreign materials, and then disappeared without evidence of further transformation. The site of the mononuclear response, on the other hand, was largely restricted to the peripheral portions of the lesion and appeared to take place largely as a migration from the normal hepatic parenchyma. Maximow² always claimed a dual origin for mononuclear exudate cells, and our observations appear to confirm this recognized concept. A certain number of these mononuclear exudate cells, we believe, arise from the lymphocytes and monocytes of the blood stream, which entered the inflammatory site, together with the neutrophils, and were found scattered throughout the lesion. The greater number, however, arose as a proliferation of the local histiocytes of the connective tissue and the Kupffer cells of the hepatic sinusoids which migrated to the lesion, there to take a position around the periphery, largely forming the delimiting capsule.

Throughout the proliferative centers around the bile ducts and blood vessels, various forms of cells without carbon could be identified. These ranged in size from small lymphocytes to the larger, typical monocyte with its reniform nucleus. These cells never contained the graphite, and we felt that all the stages in the development of the monocyte from the lymphocyte, an interpretation sustained by Bloom,¹² might be identified in these rapidly proliferating centers. To be sure, the migration of these granulocytes from the blood stream might not be excluded. It is reasonably certain, however, that the macrophages which we encountered in the hepatic parenchyma and in the periportal spaces did not form monocytes, but continued as wandering histiocytes or polyblasts until they transformed into fibroblast-like cells. The nonstoring mononuclear cells which we so often encountered, fixed or free in the sinusoids, probably did not give rise to monocytes, but continued as free wandering cells into periportal spaces as polyblasts. Bloom³ favored the interpretation, however, that these nonphagocytic endothelial cells of the liver might produce hemocytoblasts and all myeloid elements.

Bloom¹² recently reported the transformation of lymphocytes of the thoracic duct into polyblasts and fibroblasts in tissue culture. An identical transformation, we feel took place in the organization of these

aseptic lesions that we induced. On the third or fourth day after operation, when the mononuclear infiltration had formed rather a firm capsule around the necrotic tissue, the formation of fibroblasts was first evident. Within the wall surrounding the lesion, many mononuclear cells elongated, sent out cytoplasmic processes which frequently bifurcated, and formed typical fibroblasts. Many of these still contained the particles of graphite, which might be identified out in the distant cytoplasmic processes. Since fibroblasts were not ordinarily phagocytic, we must conclude that these spindle-shaped, graphite-containing cells were derivatives of the phagocytic cells of the hepatic sinusoid. Those fibroblasts which arose within the connective tissue capsule, devoid of graphite, were derivatives of the mononuclear cells, the lymphocyte, monocyte or polyblast, which had migrated into the inflammatory lesion from the periportal spaces.

SUMMARY

On the basis of a study of a series of inflammatory lesions in the livers of rats previously given moderate injections of a suspension of graphite to delineate the Kupffer cells, we believe that the Kupffer cell is not an ordinary endothelial cell, but rather a connective tissue cell of the histiocytic series. We question whether typical capillary endothelium exists in hepatic sinusoids.

Following phagocytosis of particles of graphite, the ingested material is agglomerated into larger granules distributed within the cytoplasm of the phagocytic cell. Within an hour following the production of an aseptic lesion in the liver, the Kupffer cells retract their processes, become swollen and spherical, and often detach themselves, as free mononuclear cells, and pass into the blood stream.

These macrophages now become free wandering histiocytes and may migrate, in some instances, to the site of the lesion, but more often to the adjoining regions around the portal spaces. At the same time, or shortly thereafter, the local histiocytes in the interlobular spaces rapidly proliferate and form many free, wandering cells or polyblasts. Typical monocytes also accumulate in these perivascular spaces and may arise as a transformation of migrated lymphocytes.

Polymorphonuclear leukocytes appear within the necrotic lesion and are exceedingly abundant after twenty-four hours. They are essentially restricted to the inner regions of the lesion, and do not change into other cells.

Mononuclear infiltration into the lesion is sufficient to form a capsule in from forty-eight to seventy-two hours after the production of the lesion. Further infiltration and transformation of these cells produce, at three weeks, a prominent, heavily carbonized wall separating the normal parenchyma from the normal tissue.

The mononuclear cells arise from two sources, from the agranulocytes of the blood stream and from the local histiocytes of the periportal tissue, including detached Kupffer cells

Fibroblasts arise from mononuclear cells which form the wall of the lesion. These fibroblasts which contain graphite are transformed macrophages, developed largely from Kupffer cells. Those fibroblasts without graphite develop from the histiocytes of the periportal spaces and the transformed lymphocytes and monocytes of the blood stream

LEUKOPLAKIA OF THE STOMACH

REPORT OF A CASE

HARRY A SINGER, M D

CHICAGO

The presence of squamous epithelium in gastric mucosa aside from its occurrence in connection with carcinoma or in the region of the cardio-esophageal junction has been, according to Borrmann,¹ repeatedly described. The descriptions alluded to deal apparently with the presence of microscopic areas of squamous epithelium more or less accidentally encountered. Thus Heilmann,² to whom Borrmann refers, described such an area, 3 mm long, in a microscopic preparation from a resected stomach, which was not detected grossly. Other authors similarly have described merely microscopic areas when they have spoken of the presence of squamous epithelium in the stomach. Herxheimer³ in his discourse on the origin of heterologous canceroid of the stomach mentioned, in addition to metaplastic cells misplaced squamous epithelial nests and groups of primitive undifferentiated cells which had persisted. Herxheimer made no reference to macroscopic groups of cells, and it can be safely inferred that he was discussing merely microscopic zones.

The presence in the stomach of islands of squamous epithelium of sufficient extent to form grossly visible plaques is apparently exceedingly rare and little known. Kaufmann⁴ in his comprehensive special pathology made no reference to leukoplakia of the stomach nor is this condition mentioned in the voluminous system edited by Henke and Lubarsch,⁵ although Konjetzny⁶ in his treatise of gastritis devoted several pages to the discussion of metaplasia of the gastric

* Submitted for publication, Nov 21, 1929

¹ Read before the Chicago Pathological Society, Nov 11, 1929

² From the Department of Medicine, University of Illinois College of Medicine

1 Borrmann, R. Geschwulste des Magens und Duodenums, in Henke and Lubarsch. Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, Julius Springer, 1926, vol 4, pt 1, pp 881-882

2 Heilmann, A. Zur Frage der Epithelmetaplasie. Wien klin Wchnschr **24** 168, 1911

3 Herxheimer, G. Ueber heterologische Cancroide, Beitr z path Anat u z allg Path **41** 348, 1907

4 Kaufmann, E. Lehrbuch der speziellen pathologischen Anatomie, ed 7 and 8, Berlin, 1922

5 Henke and Lubarsch (footnote 1, editions 1926-1928)

6 Konjetzny, G. Die Entzündung des Magens in Henke and Lubarsch (footnote 1, pp 768-1116)

epithelium A thorough search of the literature led to the discovery of only one report of a case of leukoplakia of the stomach, and even here, although lengthy, the title does not include any statement which refers to the leukoplakia *per se*

The aforementioned case, which was reported in 1899 by van Leersum and Rotgans,⁷ concerns a young woman 22 years of age who dated her condition to seven years prior when she was required to remain in bed three weeks on account of gastric symptoms She found it necessary in the course of time to eliminate rough foods and to restrict her diet more and more until finally she could tolerate only liquids If she attempted to eat semisolid or solid foods, pain and vomiting ensued It was stated that there was nothing in the physical examination or the history to point to syphilis except possibly the small stature of the patient whose measurements were those of a 13 year old girl In the Ewald meal yeast cells, large bacilli and other bacteria were found There was no free and 16 degrees total acidity In the stomach washings, squamous epithelial cells were present in such large numbers and groups as to cover at times the entire microscopic field Retained food was also recovered by lavage The introduction of 200 cc of fluid elicited pain and vomiting Two operations were performed, the first a pyloroplasty, the second a total extirpation of the stomach with an anastomosis of the cardia to the duodenum The distal two thirds of the stomach was transformed into a narrow tube, and the proximal one-third also was constricted but to a lesser degree As nearly as can be determined from the description, the leukoplakia was noted in all parts of the stomach, although the exact extent is not stated In two illustrations accompanying the article, stratified epithelium is seen to form the lining of the stomach wall

In a recent article on gastric syphilis, I⁸ submitted a detailed account of a case in which the resected portion of the stomach presented among other features a prominent white patch of squamous epithelium This plaque was merely touched on in the description and only incidentally mentioned On account of the rarity of this observation, a separate report seems warranted in order that the case may be indexed under the title of leukoplakia of the stomach and an adequate description of the condition be placed on record

7 Van Leersum, E C., and Rotgans, J. Extirpatie der geheele maaglooze Oesophago-Duodenostomie Endogastritis obliterans De maaglooze Mensch, Nederl Tijdschr v Geneesk **35** 993, 1899

8 Singer, H A. Syphilis of the Stomach with Special Reference to Its Relationship to Limitis Plastica, Am J Syph **13** 391, 1929

REPORT OF CASE

History—R M, a white man, 51 years of age, entered the Research and Educational Hospitals, March 22, 1928, with complaints of abdominal pain and vomiting of three years' duration. The progress of the disease was rather slow, particularly in regard to the vomiting, until shortly before entrance, when the patient was unable to retain even liquids. No history of a primary syphilitic lesion was obtained. Physical examination, except for a moderate degree of emaciation and a sense of resistance in the epigastrium, was negative.

Laboratory Data—The fasting stomach contained 120 cc of clear fluid which gave a negative test for free acid and a positive test for chemical blood. Following an Ewald meal, 450 cc of poorly digested gastric contents was obtained, which was likewise devoid of free acidity. Occult blood was present in the stomach contents and also in the two stools examined. The x-ray picture showed an hour-glass constriction and canalization of the middle portion of the stomach. There was marked gastric stasis. The roentgenologist diagnosed probable carcinoma and suggested the possibility of syphilis. There was a moderate secondary anemia. The Wassermann and Kahn tests were reported positive (four plus).

Clinical Course—After a few days of treatment with mercury and iodides, it soon became clear that the obstruction would eventually demand surgical intervention. Operation was therefore decided on. At the laparotomy, a thickened, shrunken stomach was found with the maximum involvement in the distal two-thirds, where many fibrous adhesions were encountered. An extensive resection was performed, leaving only the proximal 5 cm of the stomach. The patient made an uneventful recovery and was discharged, April 21, 1928, in good condition. He appeared a year later in the clinic complaining of an independent condition and stated that since leaving the hospital he had experienced no gastric symptoms.

Gross Pathologic Observations—The resected stomach was submitted to Dr R H Jaffe, whose anatomic diagnosis was probable syphilis of the stomach. The gross characteristics can be described in brief as follows. The specimen had the appearance of a sausage with an enormously thickened, rigid wall. There was a deep constriction 25 cm from the distal end, which produced an hour-glass deformity of the pyloric portion. The lumen of the stomach was greatly constricted, admitting in its widest part no more than two fingers. In its narrowest portion, which was located in the pyloric region, the diameter of the lumen was reduced to 0.4 cm. The maximum thickness of the wall of the stomach was 1.5 cm, the minimum, 0.9 cm. The thickening was due mainly to an increase in the submucosa, which in places measured as much as 1 cm. On cross-section the submucosa was glistening white and fasciculated. Fibrous extensions from the submucosa passed into and divided the underlying muscularis propria, giving the latter a lattice-work appearance. The serous covering and the mucous lining were slightly thickened, as seen in cross-section. The serosa on the anterior surface was roughened by adherent fibrous tags, whereas the posterior surface was smooth and glistening.

The appearance of the interior of the stomach was unique (fig 1). In the proximal end of the specimen on the anterior wall was a raised, roughly quadrangular plaque (A), which measured 2 cm and which by virtue of its snow-white color stood out prominently. The surface of this white plaque was finely wrinkled and puckered. Here and there, a radiating series of delicate folds emanated from a central depression. A small hemispherical yellowish nodule projected above the level of the plaque (this nodule which was included

in the portion removed for section consisted of fibrous tissue) The demarcation of the white plaque from the surrounding tissue was distinct A diverticulum-like outpouching (*B*) appeared distal to the described patch and was separated from it by a linear zone of superficial ulcerations overlaid by fibrin The remainder of the mucosa was for the most part mammillated and from gray-pink to pinkish red

Microscopic Description of the Leukoplakia—When the zone of squamous epithelium was approached (fig 2), the mucosa exhibited a moderate diminution in the number of glandular elements In the tunica propria adjoining the patch of leukoplakia were numerous eosinophils, round cells and plasma cells, scattered among which were enormous numbers of Russell bodies The transition between the cylindric and squamous types of epithelium was an abrupt one The squamous layer assumed its maximum thickness of from 15 to 20 cells practically immediately, but did not maintain this thickness throughout its extent



Fig 1—The distal portion of the resected stomach opened along the middle of the posterior wall A patch of leukoplakia (*A*) is separated from a localized outpouching (*B*) of the gastric wall by a linear zone of superficial ulcerations The dotted lines indicate the extent of the plaque before a piece was excised for microscopic examination

The lowermost layers of prickly cells presented a normal appearance, but those more superficially situated were swollen, poorly stained and devoid of intercellular protoplasmic bridges, but still retained their nuclei The edematous epithelial cells were found in varying numbers in different portions of the plaque The thickness of the squamous epithelial layer was directly proportionate to the size and number of the parakeratotic cells The rete pegs were on the whole poorly developed and frequently entirely absent Here and there, the squamous epithelium had undergone destruction In one area, the defect was occupied by a plug of fibrin in the meshes of which were enclosed many leukocytes and a great deal of nuclear debris Bordering such an ulcer was young granulation tissue

infiltrated by many round cells and plasma cells, eosinophilic and neutrophilic leukocytes and a few macrophages

The basal layer of the stratum germinativum rested in most places on a somewhat edematous fibrous tissue which divided and separated the muscle bundles of the greatly hypertrophied muscularis mucosae. There was little infiltration of inflammatory cells in the subepithelial connective tissue, except at the margin of the transition from the columnar type and about the areas of ulceration. In some places intervening between the squamous epithelium and the muscularis mucosae was a wide tunica propria containing glandular elements between which



Fig 2—A section from the margin of the plaque illustrating the abrupt transition from cylindric to squamous epithelium

were numerous inflammatory cells and Russell bodies. Occasionally, a gastric pit was seen communicating with the lumen of the stomach (fig 3)

Microscopic Features of the Remander of the Stomach—The mucosa showed moderate atrophy of the glandular elements, diffuse cellular infiltration and multiple superficial ulcerations bordered by dense cellular infiltrates and young granulation tissue rich in capillary blood vessels

The muscularis mucosae showed enormous increase in both the fibrous and the muscular elements and extensions of connective tissue into the overlying mucosa

The microscopic features of the submucosa were prodigious thickening due to fibrous tissue overgrowth, thickening of the larger blood vessels due mainly

to muscle fiber proliferation in the region of the adventitia, focal panvasculitis affecting the veins to a far greater degree than the arteries, perivascular round cell infiltration of varying extent, and focal and diffuse round and plasma cell infiltrations

In the muscularis propria were observed extensions of connective tissue from the submucosa invading and partially replacing the circular layer and mild infiltration along the fibrous septums

Microscopically, the serosa showed slight connective tissue thickening with minor degree of cellular infiltration



Fig. 3—Squamous epithelium overlies tubules of the gastric glands and borders the mouth of a pit

Bacteriology—Levaditi and Ziehl-Neelsen stains were negative, respectively, for spirochetes and tubercle bacilli

COMMENT

The problems in connection with leukoplakia of the stomach differ in no essential from the questions concerning leukoplakia elsewhere. The origin of the squamous epithelium in the case here reported in view of the presence of a gastritis is presumably metaplastic the result of

prolonged irritation (see Futterer⁹) It is also conceivable that the plaque originated from a group of primitive cells which possessed potentialities for differentiating into both the cylindric and the squamous types of epithelium which were simultaneously present The rôle of syphilis is conjectural The presence of syphilis was established in the case here reported In the patient of van Leersum and Rotgans,⁷ the only symptom or sign suggestive of syphilis was the lack of physical development However, the contracted state of the stomach which led to the operation might well have represented the healed stage of a syphilitic gastritis The relationship of leukoplakia to squamous cell carcinoma of the stomach involves the same considerations as leukoplakia elsewhere in the body

⁹ Futterer, G Experimentally Produced Genuine Epithelial Metaplasia in the Stomach, *J A M A* **43** 1129 (Oct 15) 1904

VARIATIONS IN THE NUMBER OF THE WHITE BLOOD CELLS ASSOCIATED WITH EXPERI- MENTAL OBSTRUCTIVE JAUNDICE *

JOHN S LAWRENCE, M D

M M HUFFMAN, M D

AND

EDGAR JONES, M D †

NASHVILLE, TENN

AND

STEPHEN J MADDOCK, M D

Fellow of the National Research Council

AND

S J G NOWAK, M D

BOSTON

A relationship between certain disorders of the liver and the monocytes in the circulating blood has been emphasized by Huffman, Lawrence and Jones¹ These investigators found that the injection of pieces of sterile macerated rabbit liver suspended in a physiologic solution of sodium chloride into the peritoneal cavities of rabbits produced increases in the number of monocytes in the circulating blood Further, they found that subcutaneous injections of phosphorus, a chemical known to be toxic to the liver, produced more marked increases in the number of monocytes in the circulating blood Prior to this, it had been shown by Jones and Minot² and by Thewlis and Middleton³ that there was an increase in the number of the circulating mononuclear cells in catarrhal jaundice in man Holt⁴ had demonstrated a similar reaction

* Submitted for publication, May 16, 1929

† From the Departments of Medicine and Anatomy, Vanderbilt University School of Medicine, the Thorndike Memorial Laboratory of the Boston City Hospital and the Department of Medicine, Harvard Medical School

† Dr Jones' participation in this work was made possible by a grant from the Henry Strong Denison Medical Foundation

1 Huffman, M M, Lawrence, J S, and Jones, Edgar The Effect on the White Blood Cells of Intraperitoneal Injection of Whole Liver, Arch Path **7** 804 (May) 1929

2 Jones, C M, and Minot, G R Infectious (Catarrhal) Jaundice An Attempt to Establish a Clinical Entity, Observation on the Excretion and Retention of the Bile Pigments, and on the Blood, Boston M & S J **189** 531, 1923

3 Thewlis, Ethel, and Middleton, W S The Leukocyte Picture in Catarrhal Jaundice (Cholangitis), Am J M Sc **169** 59, 1925

4 Holt, R B Effect on White Blood Cells in Rabbit by Ligation of Common Bile Duct, Proc Soc Exper Biol & Med **24** 974, 1927

in experimental obstructive jaundice in the rabbit. Accordingly, it seemed advisable to investigate this problem with particular reference to the relationship between jaundice and monocytosis. Holt did not produce complete obstruction to the flow of bile, since he ligated only one of the hepatic ducts. This procedure was followed by an increase in the number of monocytes in the circulating blood. We have produced experimental obstructive jaundice, both complete and partial, in a series of dogs and guinea-pigs. In general, complete obstruction was associated with only slight increases in the number of monocytes in the circulating blood, whereas partial obstruction was associated with more definite increases in the number of these cells.

EXPERIMENTAL METHOD

The observations were made on fifteen dogs and nine guinea-pigs. In all of these animals there was produced partial or complete mechanical obstruction to the passage of bile from the liver to the duodenum.

In ten of the fifteen dogs, the common duct was ligated at two places and resected between the points of ligation. In three of the dogs, the common duct was ligated at one place only. In the remaining two dogs, one of the hepatic ducts was ligated.

Postmortem examinations of all the animals were made at the end of the period of investigation. Particular attention was paid to the following points:

- 1 Evidence of complete obstruction to the flow of bile. This was determined by the position of the ligature, the passage of a probe along the common duct to the point of ligature and, finally, by pressure on the distended gallbladder or the common duct and observation on the distal side of the ligature to determine whether any bile passed the point of obstruction.

- 2 Signs of infection of the peritoneal cavity. Infection was always looked for macroscopically, and cultures were taken whenever the animal had not been dead too long to render cultures unreliable. Unfortunately, five of the animals (dogs no 1, 4, 5, 7 and 8) died several hours before autopsy, and no culture was obtained from the peritoneal cavity of any of these.

- 3 The presence of bile in the peritoneal cavity.

On the basis of these three conditions, the fifteen dogs were divided into four groups.

Group 1 includes dogs no 4, 8, 10 and 12. These animals had complete obstruction of the common duct without evidence of peritonitis and with no free bile in the peritoneal cavity. Cultures from the peritoneal cavity of two of the animals (dogs no 10 and 12) were negative. We failed to make cultures from the other two.

Group 2 includes dogs no 2, 6, 7 and 14 in which there was partial obstruction to the flow of bile, no evidence of infection of the peritoneal cavity and no free bile in the peritoneal cavity. Dog no 14 was living and in good condition at the end of the observations. The bilirubin content of the blood of this dog was consistently low, indicating that the ligation of one of the hepatic ducts produced only partial obstruction to the flow of bile. In the other three animals, the common duct was ligated at one place only, and at autopsy the obstruction to the flow of bile was found to be incomplete.

Group 3 includes dogs no 1, 3, 5, 11 and 13, all of which had had the common duct ligated and sectioned, except dog no 13, which had had a single hepatic duct ligated. These animals had infection of the peritoneal cavity and considerable elevation of the bilirubin content of the blood.

Group 4 includes only two animals (dogs no 9 and 15). In these dogs there was bile in the peritoneal cavity without evidence of infection. In dog no 9, the common duct was ligated at two places and sectioned between ligatures, but the proximal ligature came off. In dog no 15, the common duct was ligated, but not sectioned. At autopsy, however, the common duct was found to be ruptured.

For each of the dogs in the four groups repeated total and differential white cell blood counts were made, according to the supravital technic, prior to operation. The smallest number of preoperative counts was two (dog no 2). The lowest number of preoperative counts for the other dogs was four and the greatest twenty-one. The latter were done on dog no 3, which was given bromsulphalein daily for fifteen days prior to operation. Following operation, daily total and differential counts were made for five consecutive days on twelve of these animals. Of the remaining three animals one (dog no 12) had three daily counts and then one count two days later, one (dog no 9) had four daily counts, another (dog no 15) had three daily counts. Total and differential counts were made at intervals of from one to two days after the first five days following operation until the animal died or was killed. The greatest number of counts made on any animal after operation was eighteen (dog no 6). The supravital technic was relied on mainly, but, in a number of instances, fixed preparations were made and stained with Wright's stain. Determinations of the icterus index and of the amount of bilirubin in the blood serum were made at intervals by the van den Bergh method. The highest values were obtained in dog no 10 in which the icterus index reached a maximum of 31.3 units and the van den Bergh test for bilirubin gave 123.3 mg per thousand cubic centimeters of blood.

In each of the nine guinea-pigs, the common duct was ligated at one place. Autopsies were always performed at the end of the period of observation, and special attention was paid to the same points that were mentioned in explanation of the procedures for dogs. These nine guinea-pigs were divided into two groups.

1 Group 1 includes guinea-pigs no 3, 4, 5, 7, 8 and 9, all of which had complete obstruction at the point of ligation, as was shown at autopsy. Guinea-pig no 9 showed a ruptured gallbladder, but this was thought to have been a terminal event. In none of these animals was there any infection of the peritoneal cavity nor any severe infection in the region of the wound.

2 Group 2 includes guinea-pigs no 1, 2 and 6, in which there was complete obstruction to the flow of bile and also severe infection. Guinea-pig no 1 had severe cellulitis of the anterior abdominal wall and localized peritonitis. Guinea-pig 2 had an infection with a gas-producing organism in the left inguinal region and possibly also peritonitis. Guinea-pig no 6 had an ulcerated area in the region of the wound on the anterior abdominal wall.

The same general plan was followed in establishing the normal total and differential counts for these animals before and after operation, as for the dogs. Determinations of the amount of bilirubin in the blood serum were made in four instances at the time of autopsy. In each case, elevated values were obtained, the highest values being found in guinea-pig no 5 with an icterus index of 10.8 and a quantitative van den Bergh test showing 27.8 mg of bilirubin per thousand cubic centimeters of blood. Studies of the blood were made daily on all the guinea-pigs of group 1 for at least five days after operation. Guinea-pig no 3 had daily blood counts for nine days after operation, this being the longest time after obstruction

of the common duct during which the blood of any guinea-pig was counted. In group 2, guinea-pig no 1 had daily blood counts for four consecutive days, guinea-pig no 2 for two days and guinea-pig no 6 for five days.

In addition to the aforementioned series of fifteen dogs and nine guinea-pigs, two control series of guinea-pigs were studied. The first control series included four guinea-pigs (guinea-pigs no 10, 11, 12 and 13). The normal total and differential white blood cell counts were established for these animals (as for the previous groups) prior to etherization. They were then subjected to ether anesthesia for thirty minutes, and following this, their total and differential white blood cell values were determined daily for five days.

The second control series (guinea-pigs no 14, 15, 16, 17 and 18) were operated on under ether anesthesia. In this operation, which occupied thirty minutes, the abdominal wall was opened and the common duct was exposed, but not ligated. In other words, practically all the steps used in ligation of the common duct were carried out. Following operation, total and differential blood counts were made daily for five consecutive days. Autopsies were performed on all the animals of this series, except guinea-pig no 17, on the eighth day after operation.

RESULTS

All the postoperative average figures here given are for the daily counts made on the five days immediately following operation, except for dogs no 12 and 15, for which only three daily postoperative counts were made, and dog no 9, for which there were four daily postoperative counts. This five-day period was used rather than the period until death because it gave a more uniform method of comparing the average blood counts of these animals and, further, because the averages obtained for this period differed but slightly from those obtained by the use of the counts up to death. There was one exception in group 3, in which the average postoperative total count increase was for this five-day period 77.2 per cent as against 129.6 per cent for the total postoperative period.

The principal observations as regards the white blood cells in the four groups of dogs were as follows:

1. An increase in the total number of white blood cells following operation. This occurred in each group, the greatest increase being in group 3 (131.7 per cent) and the smallest increase being in group 1 (83.1 per cent).

2. An increase in the absolute number of neutrophils in each group, this increase being definitely greater proportionately than that of the total white blood cell count. The greatest rise was in group 4, in which there was an increase of 228.7 per cent. The smallest increase occurred in the animals of group 2 (129.4 per cent).

3. A diminution in the number of eosinophils in the dogs of each group. The greatest decrease occurred in group 4 (87.9 per cent). The next lowest drop occurred in group 2 (55.7 per cent).

4 A slight diminution in the number of lymphocytes in groups 1, 3 and 4, the greatest decrease being found in group 4, in which there was a diminution of 19.8 per cent. Group 2 showed an increase of 54.3 per cent.

5 An increased absolute number of monocytes in groups 1, 2 and 3 but a diminished number in group 4. The rise in group 1 was small (9.9 per cent). The greatest increase was in group 3 (136.6 per cent). In group 2 the rise was 50.5 per cent. The diminution in group 4 was 26.2 per cent.

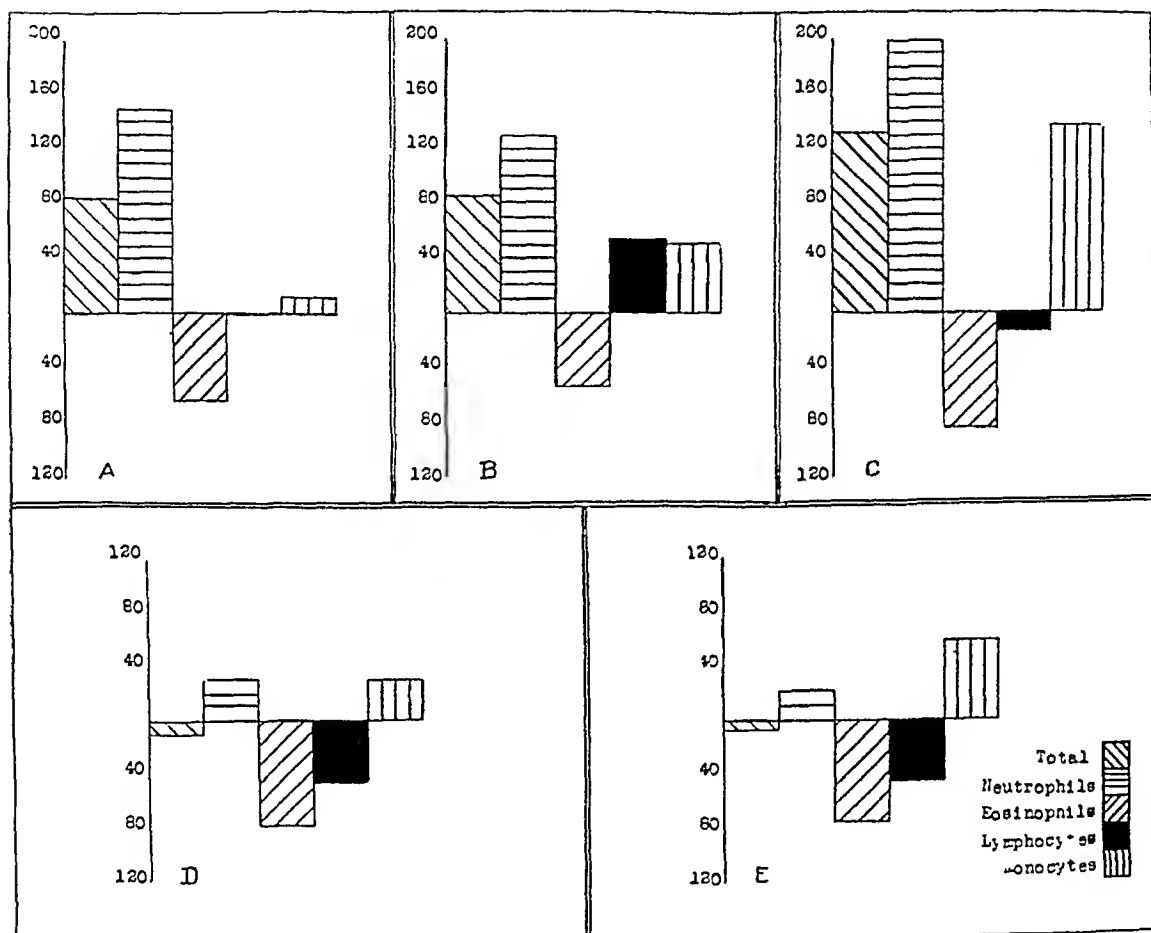
In group 1, the changes in lymphocytes and monocytes were well within the limits of normal variation, the average preoperative absolute number of lymphocytes being 1,643 per cubic millimeter, as against 1,619 per cubic millimeter for the postoperative period. The average number of monocytes prior to operation was 1,876 per cubic millimeter, as against 2,061 per cubic millimeter following operation. There was, however, an appreciable increase (83.1 per cent) in the total count and in the number of neutrophils (147.9 per cent). Again, the eosinophils showed a drop of 62.9 per cent, the average preoperative number being 1,563 per cubic millimeter and the average postoperative number being 580. In the chart, section *A* represents the percentage variations in the blood counts of the animals of group 1. In group 2 there were two main differences in the results as compared with those in group 1, namely, the lymphocytes showed an increase (54.3 per cent) from 1,102 per cubic millimeter to 1,701 per cubic millimeter, and the monocytes were increased (50.5 per cent) from 1,960 per cubic millimeter to 2,950 per cubic millimeter. Section *B* represents the percentage variations in the blood counts of the animals of this group. In group 3, the main deviation from the blood counts in group 1 is an increase in the average number of monocytes from 1,976 per cubic millimeter before operation to 4,675 (136.6 per cent) per cubic millimeter after operation. The greatest increase was in dog no. 13 in which the preoperative average was 1,984 as against 6,656 per cubic millimeter after the operation. Section *C* represents the percentage variations in the white blood cell counts of the animals of this group. In group 4, the only important variation from the counts found in group 1 was a drop of 26.2 per cent in the number of monocytes, the average preoperative count being 2,245 per cubic millimeter and the average postoperative count being 1,657 per cubic millimeter.

Six of the dogs died spontaneously. The remaining nine were killed. The longest period during which any of the animals was kept under observation following operation was twenty-one days (dog no. 6). The shortest period was three days (dog no. 15).

The essential changes in the blood of the guinea-pigs following experimental obstruction to the flow of bile through the common duct were

1 A slight increase in the number of neutrophils in the presence of a slight decrease in the total number of white cells

2 An appreciable drop in the number of eosinophils in group 1 (78.4 per cent) and in group 2 (76.2 per cent)



The variations in the numbers of the white cells of the blood in experimental obstructive jaundice. *A* The average percentage variations from normal in the numbers of the white blood cells of dogs following complete experimental obstruction to the common duct, no peritonitis or free bile being evident in the peritoneal cavity at the time of autopsy (group 1). *B* The average percentage variations from normal in the numbers of the white blood cells of dogs following partial biliary obstruction, no peritonitis or free bile being present in the peritoneal cavity at autopsy (group 2). *C* The average percentage variations from normal in the numbers of the white blood cells of dogs, following operation, peritonitis and jaundice being found at autopsy (group 3). *D* The average percentage variations from normal in the numbers of the white blood cells of guinea-pigs following complete biliary obstruction without severe infection (group 1 with guinea-pig no. 5 omitted). *E* The average percentage variations from normal in the numbers of the white blood cells of guinea-pigs following complete biliary obstruction in the presence of severe infection (group 2).

3 A similar but less marked drop in the number of lymphocytes in group 1 (46.4 per cent) and in group 2 (45.3 per cent)

4 An increase in the number of monocytes in both groups. If guinea-pig no 5 is omitted from group 1, the average increase is 28.5 per cent but if this animal is included it is 66.5 per cent. In group 2 the increase is 57.8 per cent.

There was no striking difference in the results of the experiments with the two groups of guinea-pigs except that there was a greater percentage rise of the monocytes in group 2 than in group 1, if guinea-pig no 5, which showed a different reaction as regards the blood from the other guinea-pigs in this group, is omitted. All the averages given are for the five daily postoperative counts, except in guinea-pig no 1, which had four daily postoperative counts and guinea-pig no 2, which had two daily postoperative counts. Section *D* shows the percentage variations in the blood counts of the guinea-pigs of group 1 (not including guinea-pig no 5). Section *E* shows the percentage variations in the blood counts of the guinea-pigs of group 2. Guinea-pig no 9 had a ruptured gall-bladder at autopsy, but this was thought to have been a final accident, since previous autopsies had revealed the likelihood of such an occurrence. Guinea-pig no 4 had a rather large necrotic area of one of the middle lobes of the liver, suggesting that the arterial blood supply to this area had been cut off.

A comparison of the amount of jaundice and the number of monocytes in the circulating blood showed absolutely no correlation between the two.

There was only one change of any degree among the control animals that were treated with ether anesthesia—namely, an average increase (52 per cent) in the number of eosinophils from 935 to 1,420 per cubic millimeter. These increases in the number of eosinophils were so irregular that it was not thought that they were due to the ether anesthesia, but rather to changes peculiar to the animals. Eosinophilic variations are likely to be great in normal guinea-pigs. The monocytes dropped (22.8 per cent) from 1,214 per cubic millimeter to 937 per cubic millimeter, whereas there was a slight increase (13.1 per cent) in the total white blood cell count and in the absolute number of neutrophils (19.3 per cent). The lymphocytes showed practically no change (2.2 per cent). All these animals were free from gross abnormalities at autopsy, except guinea-pig no 10 which had an adherent pleura at the left base of the lung.

The second control series of animals, that is, the series consisting of animals that had had an exploratory laparotomy, showed no changes of note in either the total or the differential white blood counts. The greatest change was in the number of neutrophils which showed an

average increase of 22.2 per cent. The percentile change in the numbers of the other white blood cell constituents of the blood was within a variation of plus or minus 10 per cent.

One of these animals (guinea-pig no. 17) had its ears badly bitten in a fight and later died. No autopsy was performed on this animal, but autopsies were performed on the four remaining ones. In all of them, the wounds of the operations were in excellent condition, and slight, if any, infection was present. The postmortem observations revealed no abnormalities, and cultures from the peritoneal cavities were sterile.

The alterations resulting from obstruction to the flow of bile through the common duct will be described in another communication. Both gross and microscopic changes from normal were noted in the liver. The changes in the livers of the guinea-pigs were much more pronounced than were those in the livers of the dogs.

COMMENT

Increases in the amount of bilirubin in the blood of the dogs with complete obstruction were not associated with equal increases in the number of monocytes in the circulating blood. There was, however, an average increase of 50.5 per cent in the number of circulating monocytes following partial biliary obstruction in dogs. This response to partial obstruction is in entire agreement with the observations of Holt.⁴ The explanation of these results offers some difficulty. It would seem that there existed a delicately balanced mechanism, slight jaundice producing monocytosis and severe jaundice causing no change in the number of these cells. Of course, one cannot assume that it is necessarily an accumulation of bilirubin or bile salts that is responsible for the reaction. It may be the cholesterol, the unsaturated fats or other less well known substances. Partial obstruction may cause the production of the optimal amount of this substance, or substances, whereas more marked obstruction may call forth too much of this unknown substance. On the other hand, complete obstruction may result in such a sudden change in the condition in the liver as to prevent the production of this "x" substance. Again, it is possible that partial obstruction may produce its result by changes in organs other than the liver. For example, it is conceivable that partial obstruction may cause changes not only in the functioning of the liver, but in the functioning of the spleen, the bone-marrow or the connective tissues. One certain fact stands out—that jaundice and monocytosis in dogs cannot be related in a quantitative fashion.

The results of the study of the series of guinea-pigs with complete obstruction corroborates the work with the dogs. There is, it is true, an average increase of 28.5 per cent in the number of monocytes in five guinea-pigs with complete obstruction, but this is not a great percentile

change for these animals and, further, the average absolute values in all these animals are within the normal limits, 1,461 per cubic millimeter being the highest average for the five-day period after operation. The highest single value occurred in guinea-pig no 7 on the third day after operation, this was 2,303 per cubic millimeter. There was distinct uniformity of the results in these five animals, but one other animal (guinea-pig no 5), with complete obstruction and no infection of the peritoneal cavity, gave a different response. The average monocyte count of this animal prior to operation was 1,185 per cubic millimeter and after operation it was 3,908 per cubic millimeter, a maximal value of 7,091 per cubic millimeter occurring on the fourth day after ligation of the bile duct. This response is so different from that of the other guinea-pigs of this series that it probably represents a different type of reaction. It cannot be stated whether this particular reaction was in the nature of an idiosyncrasy of this guinea-pig or whether it was due to some factor which was not recognized. Certainly, there is no marked response on the part of the monocytes in the blood of dogs or guinea-pigs to the production of jaundice by mechanical obstruction of the common duct.

The changes in the number of white blood cells in the presence of peritonitis in dogs and severe subcutaneous infection in guinea-pigs are of interest. In both animals there was a distinct rise in monocytes with infection. The number of these cells showed an average increase of 136.6 per cent in infected dogs, and of 57.8 per cent in the three infected guinea-pigs. The explanation of a pronounced increase in the number of monocytes in the presence of peritoneal infection remains obscure, but has been noted before by Huffman, Lawrence and Jones¹. It certainly is not due to leukocytosis per se, since there was an average increase of 83.1 per cent in the total number of white blood cells in the dogs of group 1, in which there was no true increase in the number of monocytes. In the three infected guinea-pigs there was an actual average diminution of 7 per cent in the total number of white blood cells after operation. It may be that only certain types of infection are responsible for this response or possibly only those animals which have been treated in certain ways—e.g., by ligation of the common duct—react in this manner.

Analysis of the changes in the number of white blood cells in each group of animals described in this paper reveals one result that is constant, namely, the diminution in the absolute number of eosinophils. The average diminution for the four groups of dogs and the two groups of guinea-pigs is 74.2 per cent. The lowest average diminution for any one group of animals (55.7 per cent) occurred in the dogs of group 2 and the maximal average diminution (87.9 per cent) in the dogs of group 4. It may be seen, therefore, that the diminution was of about the same range in all these animals. The explanation is not obvious.

Whether it is the bilirubin, the degeneration of the liver, the bile salts, the unsaturated fats, the cholesterol or other factors is unknown. Certain it is that experimental obstructive jaundice in guinea-pigs and dogs produces a marked diminution in the number of eosinophils. That the diminution in the number of eosinophils, in guinea-pigs, at least, is not the result of ether anesthesia or operation is conclusively shown by the two control series of animals. There was actually an increase in the number of eosinophils in both control series of guinea-pigs, which is in contrast with Krumbhaar's⁵ observations that in dogs the eosinophils are diminished in number following various surgical operations under ether anesthesia. Chadbourne⁶ (1899) found an increase in the number of eosinophils in patients following operations in which ether narcosis was used. Stahl⁷ (1921) and Garrett⁸ (1928) both found a diminution in the number of eosinophils in persons soon after surgical operations. Foote and Selinger⁹ (1927) were unable to find any changes of note in the number of eosinophils in an analysis of 147 postoperative leukocytoses following tonsillectomy. The reports in the literature, therefore, are confusing. It is probable that certain types of operations may produce a drop in eosinophils, whereas others may not. Trauma, infection and necrosis may all play a part. Since all the external conditions of the control and the ligated series of guinea-pigs were as nearly identical as possible, with the exception of ligation in the one group, it would seem that the marked diminution in the number of eosinophils in these animals was in some way associated with the peculiar changes resulting from ligation of the common duct. One cannot assume, however, that these changes were specific, since a diminution was found by us in dogs in other postoperative conditions. The jaundice is probably not an important factor, since patients with jaundice may show an appreciable number of eosinophils, particularly in the presence of pruritus.

There was also a diminution in the number of the lymphocytes in all the animals except the dogs of group 2, in which there was an average increase of 54.3 per cent. The average diminution (25.4 per cent) for the five other groups of dogs and guinea-pigs was much less than the decrease in the number of the eosinophils. Also, the variations in per-

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9 Foote, J. A., and Selinger, Maurice. Postoperative Leukocytosis and Temperature Variations Following Tonsillectomy. An Analysis of 147 Cases Arranged in Four Age Groups, *Am J Dis Child* **33** 96, 1927

centage change were much greater, there being a decrease of only 0.4 per cent in group 1 of the dogs and of 46.4 per cent in group 1 of the guinea-pigs. With these wide fluctuations, it does not seem that the changes in the number of lymphocytes were of as much significance as those in the number of the eosinophils.

The changes in the total number of white blood cells and neutrophils were constant for the four groups of dogs, showing an increase in each group. These results may, in part, have been due to localized infection. In both series of guinea-pigs, however, the number of neutrophils was increased slightly, but the total number of white blood cells was diminished. The leukopenia may have been due to the more profound disturbances of the organism in the case of the guinea-pig.

CONCLUSIONS

Complete, sudden obstruction to the common duct in dogs and guinea-pigs, in the absence of severe infection, produces only slight increase in the number of monocytes in the circulating blood, whereas partial biliary obstruction in dogs produces a slightly greater increase in the number of monocytes in the blood. Complete or partial sudden obstruction to the common duct in the presence of severe infection in dogs or guinea-pigs is associated with a definite increase in the number of circulating monocytes.

There is a constant and marked diminution in the number of eosinophils in dogs and guinea-pigs with complete or partial experimental biliary obstruction. The operation per se does not explain this response in the guinea-pig.

The response of the lymphocytes to obstructive jaundice experimentally produced in dogs and guinea-pigs is inconstant.

A postoperative neutrophilic leukocytosis occurs in dogs after experimental biliary obstruction, whereas a leukopenia occurs in guinea-pigs after a similar procedure.

EFFECT OF CERTAIN TOXIC SUBSTANCES IN BACTERIAL CULTURES ON THE INTESTINAL MOVEMENT

III THE EFFECT OF THE PHYSIOLOGICALLY ACTIVE SUBSTANCES OF THE GAS BACILLUS ON THE MOVEMENT OF THE INTESTINE IN THE INTACT ANIMAL *

E E ECKER, PH D
AND
D E SCHNEIDER, B A
CLEVELAND

In a recent communication, Kendall and Schmitt¹ reported the finding of a physiologically active (histamine-like) substance in filtrates of carbohydrate medium cultures of the gas bacillus which (1) caused immediate contracture of the isolated strip of intestine of the guinea-pig, and (2) a transient drop of blood pressure when the filtrate was injected into the vein of a dog. The substance was not obtained from culture mediums from which carbohydrate was excluded, but from mediums in which fermentation was active, the substance was present in considerable—nearly maximal—amount in forty-eight hours. The substance was heat stable and was antagonized successfully by a titration using solution of formaldehyde, which indicates its content of free aromatic ethylamine groups as in histamine. Certain aldehydes known to react with aromatic amines also showed neutralizing effects, while ketones and other aldehydes did not.

These observations led us to the study of this substance or substances in the intact animal by the method recently described by Ecker and Biskind²

METHOD

Two mediums were employed (1) skimmed milk and (2) sucrose veal infusion Witte peptone broth of pH 7.2. Fifty cubic centimeters of each of the

* Submitted for publication, Nov 25, 1929

* From the Institute of Pathology, Western Reserve University

1 Kendall, A. T., and Schmitt, F. O. Proc. Soc. Exper. Biol. & Med. **24** 104, 1926. Kendall, A. T. Ibid **24** 316 and 493, 1926. Kendall, A. T., and Alexander, H. L. Ibid **24** 894, 1926.

2 Ecker, E. E., and Biskind, M. S. Effect of Certain Toxic Substances in Bacterial Cultures on Intestinal Movement, Effect of Filtrate of Young Cultures of Colon-Typhoid Group of Organisms on Intestinal Movement of Rabbits as Recorded by New Cinematographic Method, Correlation of This Effect with Production of Food Poisoning by Members of This Group, Arch. Path. **7** 204 (Feb.) 1929.

mediums was placed in each of a series of test tubes measuring 20 cm by 2.5 cm in order to have a high column and to secure anaerobiasis. The mediums were then inoculated with a strain of the gas bacillus (obtained through the courtesy of Dr. Ivan Hall). The tubes were then placed at 37 C., and the organisms allowed to grow for various periods of time. In the case of the milk cultures, the separated whey was filtered through a Berkefeld N candle, while the broth cultures could be passed directly through the candle. The milk cultures showed stormy fermentations. Prior to the intravenous injection of the filtrates into the animals, the filtrates were carefully neutralized to a pH of 7 with tenth-normal sodium sodium hydroxide.

The whey control was obtained by clotting the skimmed milk with butyric acid, and neutralizing the acid with tenth-normal sodium hydroxide. The original neutral sterile filtered sucrose broth was used as a broth control in the series of animals into which the filtrates of the sucrose broth cultures were injected.

The preparation of the animals (rabbits) was the same as that described by Ecker and Biskind. As further controls, a series of normal rabbits received the same doses of the filtrates intravenously and their reactions were carefully observed.

EXPERIMENTS

Table 1 shows the effect of the filtered whey from skimmed milk cultures of various ages.

In this series of experiments, six of the nine control rabbits died in prostration or convulsions in eighteen hours or less. Soft stools were obtained in three of the animals, the intestinal reactions being mild as compared with those obtained with filtrates of cultures of the paratyphoid (*actycke* type) and *B. enteritidis* group of organisms.

The laparotomized animals into which the whey filtrates of cultures sixty-six hours old were injected showed an increase of rhythmic longitudinal muscle movements (pendulum) with localized circular spasms and filling of the ileum. When, however, the whey filtrates of five day cultures were employed, the pendular movements extended to the duodenum and jejunum. Here, also, localized areas of spasms were noted. The same reactions also occurred with employment of whey filtrates of nine day and fourteen day cultures. The neutral whey filtrate control did not produce noticeable changes.

Table 2 shows the effect of the filtered sucrose broth cultures of various ages.

The control rabbits into which were injected the filtrates of the toxic sucrose broth cultures showed depression, prostration, labored respiration and occasionally soft stools. The symptoms appeared usually in about one-half hour after the injection of the filtrates. All the animals recovered completely within twenty-four hours.

In this series, the laparotomized animals showed marked pendulum movements and localized circular spasms of the duodenum and jejunum when filtrates of twenty-four hour cultures were given by vein. As filtrates of the older cultures were injected (five day cultures), the

TABLE 1—Results of Injection of Filtrates of Skimmed Milk Cultures of the Gas Bacillus Into Lopharotomized Rabbits

Age of Culture	Dose, Rabbit, Cc*	Weight of Rabbit, Gm	Results**					Control Normal Rabbit, Gm		Results in Control Normal Rabbit**
			Duodenum and Jejunum		Ileum	Cecum	Colon	Rectum		
66 hr	2	2,000	Quiescence		23' slight increase of pendular motion with localized circular spasm and filling	Quiescence	Quiescence	Quiescence	2 050	1 hr soft stool apparently normal conditions
96 hr	1	1,973	Quiescence		32' slightly increased pendular motion					2 hr convulsions and death
5 days	2	1,880	13' increased pendular motion with filling		38' filling, pendular motion, propulsion			10' expulsion following spasticity	2,100	1 hr soft stool, weakness
			20' localized circular spasm		47' localized circular spasm	50' mild contractions		60' expulsion	2 250	18 hr recovery
5 days	18	2,100	10' 25' only slight pendular movement†		10' 25' slight pendular movement	Quiescence	Quiescence	Quiescence	1,680	52' partly nodular, partly soft stool
5 days	18	2,650 (pregnant)	15' slight pendular movement†		20' slight pendular motion					107' marked symmetrical convulsions, opisthotonus, respiratory failure, death
5 days	1	1,710	25' filling, slight pendular movement		23' filling, pendular motion	Quiescence	Quiescence	45' expulsion		10' hyperexcitability
			32' circular bands, tendency to propulsion		34' increased pendular motion			pulsion		25' jerky respiration
			30' marked local circular spasm		50' spastic circular arcs	Quiescence	Quiescence	Quiescence	1,850	15' prostration
5 days	1	1,900	0' distention with gas		15' slightly increased pendular motion					18 hr death
			1' gas distention causing increased pendular motion			1' distention			2 200	15' depression
			25' 30' localized circular spasticity, increased pendular motion			15' slight cecal motion	1' distention	20' expulsion		30' excitability, jerky, rapid respiration
9 days	2	2,175	27' increase (slight) of pendular motion		27' slightly increased pendular motion					18 hr recovery
					52' occasional filling		67' marked spasticity		2,050	
14 days	2	1,710	105' increase (slight) of pendular motion		10' arcs of local spasm, increased pendular motion	Quiescence	Quiescence	60' expulsion	2 375	1 hr excitability, defecation tremors, prostration
										18 hr convulsions, death
Control (when filtrate neutralized with butyric acid)	2	1,875	Quiescence		Quiescence	Quiescence	Quiescence	Quiescence	2 350	10' depression, respiration jerky
										1 hr Prostration
										18 hr death
										Quiescence normal

* All filtrates neutralized to pH 7 at injections All injections intravenous
** Time given is time after injection
† 45' animal died

* All filtrates neutralized to pH 7 at injections
 ** Time given is time after injection
 † 45' animal died on board in asphyxial convulsions
 ‡ 30' rhythmic contraction of uterus bloody vaginal discharge, death on board in 90 minutes, in asphyxial convulsion
 § 1 cc injected into lumen, no toxic effect

TABLE 2—Results of Injection of Filtrates of Sucrose Broth Cultures of the Gas Bacillus Into Laparotomized Rabbits

Age of Culture	Dose, Rabbit, Grams	Results					Weight, Control Normal Rabbit, Grams	Results in Control Normal Rabbits	
		Duodenum and Jejunum	Ileum	Cecum	Colon	Rectum			
24 hr	2	2½ marked pendular movement 25½ localized areolar spasm	Same as in duodenum	20½ slight contractions		¾ ex-pulsion, contractions	1,850	2½ slight depression 35½ normal conditions 18 hr recovery	
48 hr	2	1½ marked pendular movement, slight filling of ileum, local areolar spasm	Same as in duodenum		25½ slight spasm		2,050	35½ slight depression 10½ more marked depression, labored respiration 18 hr recovery	
72 hr	2	60½ filling of entire small intestine, localized areolar spasm, increased pendular motion	Same as in duodenum			60½ ex-pulsion	1,600	60½ marked dyspnea 70½ prostration and opisthotonus, seemingly almost in death 18 hr recovery	
5 days	2	1½ circular spasm, marked pendular motion in entire small gut, most marked in ileum	15½ localized peristalsis	35½ slight contractions			1,780	20½ slight depression 30½ prostration 18 hr recovery 3 days later death	
5 days	3	10½ increased pendular motion in entire small gut, marked ileic spasticity	Same as in duodenum		50½ slight spasticity	5½ filling with gas	2,000	15½ depression 15½ prostration 18 hr recovery	
8 days	2	35½ filling, increased pendular motion 10½ marked filling, pendular motion and peristalsis	35½ increased pendular motion 40½ peristalsis				2,000	25½ depression 15½ prostration 6½ prostration and opisthotonus 18 hr recovery	
8 days	2	20½ increased areolar spasm 30½ increased pendular motion and peristalsis	20½ increased pendular motion, filling 30½ marked filling, marked peristalsis 55½ mild rush (incomplete)				1,550	20½ depression, labored respiration 40½ prostration 60½ soft stools, continued depression 18 hr recovery	
Sterile control	2	Only slight pendular motion	Practically complete quiescence				2,900 (pregnant)	No effect	
5 days	20, by stomach tube	0½ marked stomach distention of feeding 20½ slight undulations of stomach wall 20½ 2 hr marked pendular motion, extreme filling, peristalsis and mild rushes	0½ distention by gas partly	0½ distention, by gas partly			2,050	0½ 2 hr apparently normal, nodular defecation	

reactions became more marked, and the circular spasms of the upper intestines became pronounced. The lower intestines showed only their usual propulsive movements. The injection of the filtrate of the sterile control sucrose broth produced nothing unusual, the normal pendular motions of the upper intestines were noted here.

Intrastomachal injection (by catheter) of 20 cc of a filtrate of a five day sucrose broth culture produced marked pendular motions with filling and peristalsis in the upper intestines. In this animal, a partial peristaltic rush was observed. Beyond defecation, nothing unusual was seen in the control animal, which received the same dose of the filtrate by stomach tube.

In both of these series of experiments little or no abnormality was noted in the reactions of the lower intestines.

In our series of experiments, a minimum of ten minutes elapsed before a noticeable change occurred in the contractions of the intestines *in situ*. The isolated strips of intestines, as used by Kendall, responded immediately to the addition of the toxic filtrate. From our experiments, therefore, it is difficult to conclude at present whether one or more toxic substances are responsible for the effects noted.

SUMMARY AND CONCLUSIONS

Rabbits into which neutral whey filtrates of from three to nine day old skimmed milk cultures of the gas bacillus were injected showed increased rhythmic longitudinal muscle movements with filling of the duodenum, jejunum and ileum. Localized areas of circular spasms were also seen. A peristaltic rush as described by Ecker and Biskind and seen in rabbits into which filtrates of broth cultures of the paratyphoid-enteritidis group of organisms were injected, was not found.

Rabbits into which filtrates of neutral sucrose broth cultures of the organism were injected showed the same reactions as those into which the toxic whey filtrate was injected, but to a more marked extent.

Control injections of neutral whey or neutral broth failed to produce the reactions.

No abnormal movements were noted in the lower intestines.

Control rabbits receiving the filtrate of the neutral toxic whey became depressed and prostrated, and showed labored respiration usually followed by death with or without convulsion within eighteen hours. The animals appeared excited. The same symptoms of intoxication were seen in rabbits into which the filtrates of the neutral toxic sucrose broth were injected, but the animals survived.

General Review

THE PATHOLOGY OF TETANUS *

IVAN C HALL, PH D

DENVER

CONDITIONS UNDER WHICH TETANUS MAY OCCUR

The natural home of the tetanus bacillus is probably in the intestinal tracts of man and animals ¹ From these sources it finds its way into the soil, but whether it multiplies in the soil is really uncertain It probably does under conditions of symbiosis with aerobic micro-organisms that reduce the oxygen tension sufficiently to provide the anaerobic requirements of the tetanus bacillus

Certainly, the great majority of cases of tetanus arise through wounds contaminated with soil, as in war,² Fourth of July injuries,³ subungual hematomas ⁴ and deep injuries of various kinds Tetanus neonatorum ⁵ is not uncommon, particularly in the tropics, it is generally due to contamination of the umbilical cord Tetanus sometimes occurs after criminal traumatic abortion,⁶ after hemostatic injection of infected gelatin,⁷ as a complication in drug inebriety ⁸ and even as a result of flea bites on the feet ⁹ The tetanus bacillus has been found in court plaster,¹⁰ but I have seen no record of tetanus following the use

* Submitted for publication, Sept 5, 1929

* From the Department of Bacteriology and Public Health, University of Colorado School of Medicine

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2 Sanford, A H Internat A M Museums Bull **7** 365, 1918 Cummins, S L, and Gibson H G Lancet **1** 325, 1919 Bruce, D Ibid **1** 331, 1919 Churchill, W Ibid **1** 725, 1919

3 Fourteenth Annual Summary of Fourth of July Injuries, editorial, J A M A **67** 676 (Aug 26) 1916

4 Berard, L, and Lumiere, A Presse med **32** 621, 1924

5 Anders, J M, and Morgan, A C Tetanus Neonatorum, J A M A **47** 2083 (Dec 22) 1906 Hill, E W Tetanus, Arch Int Med **8** 747 (Dec) 1911

6 Schneider, G H Centralbl f Bakteriol (Ref) **87** 222, 1927

7 Anderson, J Hygienic Laboratory Bulletin, no 9, 1902

8 Doane, J C Tetanus as a Complication in Drug Inebriety, J A M A **82** 1105 (April 5) 1924

9 Rohardt, W Centralbl f Bakteriol (Ref) **87** 222, 1927

10 McCov, G W, Leake, J P and Corbitt, H B Pub Health Rep **32** 1450, 1917

of court plaster. A few cases of tetanus following extraction of teeth have been recorded,¹¹ and I once recovered the tetanus bacillus from the mouth of a healthy child.¹²

A number of cases of tetanus have followed smallpox vaccination, due, in some of the earlier instances before adequate methods of controlled manufacture were in vogue, to contaminated viruses,¹³ to the use of bunion pad dressings¹⁴ and to careless contamination of the vaccination sore by the patient himself. Francis,¹⁵ Geiger¹⁶ and others have shown that the danger of tetanus following vaccination with good virus, properly applied and cared for, is practically negligible.

Tetanus following surgical operations always presents an interesting problem because the question generally arises as to the source of the organisms, whether from catgut or from the intestinal tract of the patient. Thus, Jaffe¹⁷ found anaerobic bacilli in a case of tetanus following an ovariectomy, but, in England, was unable to make animal tests. Huggins¹⁸ pointed out that while "catgut has been looked on with a good deal of suspicion, there are few cases in fact where it (tetanus) has been definitely traced to catgut" and urged the view that the intestine is the real origin in many cases. Patton,¹⁹ on the contrary, held that suture material is the common source of postoperative tetanus and observed that there is no record of a case of tetanus complicating typhoid fever. Neither is there any record of tetanus following submucous resection of the nasal septum, which would seem to exclude all as a possible source of the organism. It certainly seems plausible that poor catgut might serve as a source of *B. tetani*, but I am inclined to concur with Huggins that it does so only rarely now. The temptation to blame the catgut in a case of postoperative tetanus is well illustrated in Dyke's case following cesarean section,²⁰ in which catgut from the same lot gave negative results. I believe that the facts in this case indicate that tetanus bacilli from the intestinal tract of the patient became localized in the sutures after operation.

11 Maranon, G., and Velarde, J. Abstr., Dental Cosmos **67** 231, 1925, abstr., J. Bact. **9** 271, 1925.

12 Hall, I. C. J. Infect. Dis. **37** 87, 1925.

13 McFarland, J. J. M. Research **7** 474, 1902.

14 Armstrong, C. Pub. Health Rep. **40** 1351, 1925, **42** 3061, 1927, Post-vaccination Tetanus and Its Prevention, J. A. M. A. **90** 738 (March 10) 1928.

15 Francis, E. Hygienic Laboratory Bulletin, no. 95, 1914.

16 Geiger, J. C. California State J. M. **15** 152, 1917.

17 Jaffe, J. I. Brit. M. J. **1** 1480, 1909.

18 Huggins, R. R. Surg. Gynec. Obst. **30** 142, 1920.

19 Patton, W. D. Canad. M. A. J. **13** 332, 1923.

20 Dyke, S. C. Lancet **2** 596, 1926.

Tetanus occurs naturally in man, in the horse²¹ and in the camel,²² and it can be reproduced experimentally in mice, rats, guinea-pigs, rabbits, fowls, goats and other warm-blooded animals. But there is considerable difference in susceptibility among these, and cold-blooded animals are insusceptible. Knorr²³ showed that weight for weight the susceptibility of horses is twice that of goats, thirteen times that of mice, 2,000 times that of rabbits and 200,000 times that of fowls. It also takes about ten times as much tetanus toxin to kill a rat weighing 150 Gm. as to kill a guinea-pig weighing 350 Gm.

INVASION OF THE TISSUES BY BACILLUS TETANI

Bacillus tetani possesses little ability to invade tissues in the body distant from the portal of entry, i. e., a wound usually, though Lacy and Murdock²⁴ recorded a rare case in which the organism was recovered from the cerebrospinal fluid. Growth is dependent on anaerobiosis, which is favored by anemia and necrosis, traumatic or otherwise. Frequently in wounds the presence of aerobic bacteria serves to favor anaerobic growth by reduction of the oxygen tension, and certainly tissue cells that have been deprived of their usual oxygen supply through the circulation may do so. Vaillard and Vincent²⁵ found that although *B. tetani* grows well at from 20 to 22 C., sporulating freely, it forms little or no toxin at that temperature, and such cultures can be injected into animals in considerable quantities without injury.

Cultures grown at 37 C., on the other hand, were pathogenic in minute doses, owing to the powerful soluble toxin, but when heated to 65 C. for twenty minutes they too became impotent in animals. Vaillard and Vincent²⁵ discovered that detoxified spores were reactivated by lactic acid, trimethylamine, "*Microbacillus prodigiosus*" or even simple trauma. Vincent²⁶ further showed that guinea-pigs inoculated with tetanus spores detoxified by heating to 85 C. for three hours, and exposed for one-half hour at 40 C., during which the animals' temperature might rise to 42 C. or more, succumbed to tetanus, while similarly inoculated control animals, not so exposed, suffered no harm. Tarozzi²⁷ found that detoxified tetanus spores might be demonstrated in experimental animals as long as three and a half months after their inocula-

21 MacConkey, A. T. Brit. J. Exper. Path. **7** 133, 1926

22 Rabaghlati. J. Comp. Path. & Therap. **33** 10, 1920

23 Knorr, A. Munchen med. Wchnschr. **45** 321 and 362, 1898

24 Lacy, G. R., and Murdock, C. J. Lab. & Clin. Med. **7** 100, 1921. Montessano, G., and Montessori, M. Centralbl. f. Bakteriologie **22** 663, 1897

25 Vaillard, L., and Vincent, H. Ann. de l'Inst. Pasteur **5** 1, 1891

26 Vincent, H. Ann. de l'Inst. Pasteur **8** 450, 1904

27 Tarozzi, G. Centralbl. f. Bakteriologie **1**, O. **40** 305 and 451, 1906

tion, but Cantoria²⁸ was able to confirm Tarozzi's observations only up to fifty-five days. In 1911, Semple²⁹ added quinine to the list of reactivating agents, and in 1914 Francis¹⁵ showed that the "washing of tetanus spores by successive suspension and centrifugalization in large quantities of saline solution did not rid them of their toxin," and that tetanus spores detoxified by heating to 80 C for one hour previous to injection might be reactivated by quinine or staphylococci up to one month in guinea-pigs and by staphylococci but not by quinine up to four months in mice.

There seems to be a marked difference in the persistence of pathogenic spores and nonpathogenic spores in the tissues of animals. Koser and McClelland³⁰ observed that the spores of nonpathogenic aerobes disappeared rapidly from the site of inoculation and from the viscera, while those of *B. tetani* and some other anaerobes were still present after several weeks or even months. Teale and Bach,³¹ in 1920, found that the washed spores of various aerobic bacilli, including *B. anthracis*, did not usually remain latent in the animal body, many being rapidly ingested and destroyed by phagocytes while others vegetated and were more slowly destroyed. *B. tetani* and *B. welchii* behaved similarly except that a small, sometimes a large, proportion did not germinate but remained latent, multiplication of washed anaerobic spores rarely occurred in the tissues. Teale and Bach found that lactic acid, ferric chloride, calcium chloride and oleum phosphorum (B. P.) given subcutaneously up to four days after the organisms and gelatin charcoal or peptone given intraperitoneally with the organisms favored infection.

In 1919 Bullock and Cramer³² showed that surface cultures and washed broth cultures in *B. tetani*, *B. welchii*, *Vibrio septique* (*B. septicus*) and *B. oedematiens* (*B. novyi*) were noninfectious for mice and guinea-pigs. Such inactivated suspensions could be reactivated by the readdition of culture fluid in amounts too small to have any effect alone on animals, which suggests the presence of Bail's agglutinins³³. Certain ionizable salts of calcium such as the chloride nitrate or acetate had a similar effect when injected either at the same time or previous to

28 Canfora, M. Centralbl. f. Bakteriologie 1, O 45 495, 1908

29 Semple, D. Scientific Memoirs of Officers of the Medical and Sanitary Departments of the Government of India, 1911, no. 3, quoted by Francis (foot-note 15)

30 Koser, S. A., and McClelland, J. R. J. M. Research 37 259, 1917-1918

31 Teale, F. H., and Bach, E. J. Path. & Bact. 23 315 1919-1920

32 Bullock, W. E. and Cramer, W. Proc. Roy. Soc., London (series B) 90 513, 1917-1918

33 Bail, O. Centralbl. f. Bakteriologie 1, O 27 517 1900, 33 343, 610 and 756, 1902 40 371, 1906

or within a few days after, the injection of the organisms. Insoluble salts of calcium, such as the carbonate, and the chlorides of sodium, potassium, ammonium and magnesium were ineffective. Strontium chloride was active with *Vibrio septique*, but only in larger doses, citrates given simultaneously with calcium ions rendered the latter innocuous, presumably by precipitation. Aqueous extracts of earth were often potent, but not always in proportion to the calcium content. Direct contact between the spores and the calcium was unnecessary, positive results were obtained when injections were made at the same time into different sites, or at different times into the same or different sites.

The action of the calcium salts was on the tissues of the body making them more favorable for the growth of the bacteria. For when toxin-free spores were suspended in a solution of calcium chloride, then centrifuged out and injected, they had not become virulent. Neither did administration of calcium chloride to the animals render them more susceptible to the action of injected toxins. But if the organism and the calcium chloride were injected separately, the disease localized where the calcium was introduced.

Bullock and Cramer designated this phenomenon as "defense rupture," or "kataphylaxis," and interpreted the distribution of tetanus and gaseous gangrene in the great war as an expression of the varying calcium content of the soil in different localities. The experimental facts also help to explain the occurrence of latent and delayed tetanus, as well as the occasional relapses following apparently successful use of antitoxin.³⁴ Russell³⁵ found that tetanus spores vegetate in the tissues only in the presence of necrosis, due for example, to trauma, earth or calcium chloride. According to Fildes,³⁶ the failure of inoculated toxin-free spores to germinate is not due to phagocytosis but to the presence of oxygen in the normal tissues. Necrotizing agents permit vegetation and toxin production by lowering the oxygen tension, i. e. by producing anemia in the tissues.

THE ACTION OF TETANUS TOXIN

I may now discuss what happens when the tetanus bacillus having found lodgement in the tissues and conditions suitable for multiplication produces its toxin. First of all, it is rare for the organism to penetrate undamaged tissues, although it should not be forgotten that associated bacteria such as streptococci, staphylococci and others may do so. Perhaps, some of the failures in the therapeutic use of tetanus antitoxin

34 Whittemore, W. L. *Tetanus* J. A. M. A. **71** 1995 (Dec. 14) 1918

35 Russell, D. S. *Brit. J. Exper. Path.* **8** 377, 1927

36 Fildes, P. *Brit. J. Exper. Path.* **8** 387, 1927

are due to lack of appreciation of the fact that other bacteria often find a foothold in the body at the same time as *B. tetani* and may cause death in spite of the protective action of the antitoxin. But the tetanus bacillus itself generally remains localized and it is the absorption of toxin from the localized focus which causes the disease. Obviously, débridement of the focus is one of the most important items both in prevention and in cure.

Ehrlich³⁷ distinguished two antigenic poisons in tetanus toxin, i. e., tetanolysin, which dissolves red blood cells in vitro, and tetanospasmin, which is responsible for the symptoms of tetanus. There is no evidence that tetanolysin is of any consequence in the natural or the experimental disease, and it may not even be produced by some strains under certain conditions. Thus, in 1912, I was producing potent tetanus toxins (from 10,000 to 20,000 minimal lethal doses per cubic centimeter)³⁸ which were absolutely nonhemolytic, yet the antitoxins resulting from the immunization of horses with them were fully protective against the test toxin supplied from the U. S. Hygienic Laboratory, which was actively hemolytic in vitro.

Nerve tissue has a marked affinity for tetanospasmin, as was demonstrated by Donitz³⁹ and by Wassermann and Takaki.⁴⁰ But this affinity is by no means peculiar to nerve tissue, Peterson⁴¹ having shown some degree of neutralization of tetanus toxin by leukocytes and fixed tissue cells of different organs of various animals such as the dog, rabbit and guinea-pig. It may be that variation in the combining abilities of the various tissues in different animals accounts in part for the marked difference in susceptibility to tetanus that is known to exist.

There have been much speculation and experimentation as to the route followed by tetanus toxin from the place of its elaboration to the site of damage. Many observations have shown that intravenous inoculation of tetanus toxin leads to generalized tetanus, while subcutaneous or intramuscular inoculations lead to localized tetanus. Zupnik⁴² distinguished between tetanus descendens and tetanus ascendens, the former being attributed to the supposed absorption of toxin by the central nervous system, particularly the spinal cord, from the circulating blood, the latter to direct absorption of the toxin by the muscles. Thus tetanus descendens would manifest itself by generalized symptoms,

37 Ehrlich, P. Berl klin Wchnschr **35** 273, 1898.

38 Hall, I. C. Univ Calif Pub Path **2** 97, 1913.

39 Donitz, W. Deutsche med Wchnschr **23** 428, 1897.

40 Wassermann, A., and Takaki, T. Berl klin Wchnschr **35** 5, 1898.

41 Peterson. Ztschr f Immunitätsforsch u exper Therap (Orig) **8** 498, 1910.

42 Zupnik, L. Wien klin Wchnschr **15** 89 1902.

tetanus ascendens, by localized symptoms Trismus and opisthotonos, which are often so conspicuous in human tetanus, were regarded as symptoms of tetanus descendens, and explained by the theory that the muscles of the neck and back are most strikingly affected because they are so much stronger than their respectively opposing groups

Vaillard and Vincent⁴³ in 1890 showed that the contractions of a particular muscular area ceased when the motor nerves leading to it were severed, and in 1892, Brunner⁴⁴ found that there was apparently no direct action of tetanus toxin on muscles isolated from their ganglionic centers Bruschettini⁴⁵ in the same year demonstrated the presence of tetanus toxin in both the central and the peripheral nervous systems after subcutaneous inoculation Milchner,⁴⁶ Marie⁴⁷ and Wassermann and Takaki⁴⁰ all showed that the toxins combined chemically with nervous tissues, as may be demonstrated by the protective action of the latter in animals inoculated with mixtures of toxin and brain substance These observations led Marie and Morax⁴⁸ and Meyer and Ransom⁴⁹ independently to discover that the toxin is absorbed by the myoneural junction and passes to the spinal nerve centers by way of the axis cylinders of the motor nerves Ransom⁵⁰ subsequently reiterated this view and emphasized that "the cells of the central nervous system do not pick up the toxin from the blood or the lymph, the only route by which the cells can be attacked is via the motor nerves The sensory nerve trunks are not implicated in the transport of toxin from the seat of injection or the blood stream to the central nervous system Nevertheless, the sensory cells are susceptible if the toxin is brought into direct contact with them Injection into a posterior root does not cause any muscular rigidity, but there is extreme hyperaesthesia in the sensory areas corresponding to the injected roots" Meyer and Ransom⁴⁹ called this "tetanus dolorosus"

There is no question that tetanus toxin often enters the circulatory blood stream In the early days of serum manufacture, before suitable safety tests such as are now required had been devised, a number of deaths from tetanus in St Louis were ascribed to tetanus toxin presumably present in the blood of a horse which supplied diphtheria

43 Vaillard, L, and Vincent, H *Semana med* **10** 425, 1890

44 Brunner, C *Berl klin Wchnschr* **28** 881, 1891, *Deutsche med Wchnschr* **20** 100, 1894

45 Bruschettini, A *Riforma med* **8** 256, 1892

46 Milchner, R *Berl klin Wchnschr* **35** 369, 1898

47 Marie, A *Ann de l'Inst Pasteur* **11** 591, 1897 *ibid* **12** 91, 1898

48 Marie, A, and Morax *Ann de l'Inst Pasteur* **18** 818, 1902

49 Meyer, H, and Ransom, F *Arch f exper Path u Pharmacol* **49** 369, 1903

50 Ransom, F *Lancet* **2** 928 1917

antitoxin⁵¹ Bailly asserted that he had confirmed a case of acute spontaneous tetanus in a rabbit by inoculation of a guinea-pig with 3 cc of the rabbit's blood, the guinea-pig also developing tetanus, and suggested the utilization of heart's blood from cadavers in proving the cause of death in suspected tetanus, but Cesari was never able to produce tetanus in mice with the blood of horses showing symptoms of tetanus while undergoing immunization⁵² While these observations seem to be contradictory to those of Bolton and Fisch,⁵¹ they are really not so, for the latter showed that the toxin disappeared from the blood stream before, or coincidently with the appearance of symptoms, Bailly's idea of diagnosing tetanus by inoculation of animals with blood secured post mortem is therefore valueless

Teale and Embleton⁵³ held that "although tetanus toxin ascends to the central nervous system by way of the axis cylinders of the nerves, it also to a very great extent passes up the nerves to the cord by way of the perineural lymphatics. Blocking of the latter paths greatly delays and in some cases completely blocks the occurrence of tetanus in the part corresponding to the nerve whose lymph path has been blocked

"Although tetanus toxin passes rapidly from the blood vessels into the connective-tissue spaces and thence to the thoracic duct the toxin does not pass from the capillaries of the central nervous system to the tissues thereof." Neither does it pass from the choroidal plexus to the cerebrospinal fluid. It is perhaps important that, "although bacteria can pass through the posterior root ganglion to the cord colloidal pigments and tetanus toxin are prevented from doing so. Iodine, although it prevents tetanus toxin from producing its characteristic effects when iodized toxin is inoculated subcutaneously or intravenously, does not affect the toxin when inoculated intracerebrally, it does not hinder the occurrence of the typical symptoms of cerebral tetanus, and there is no apparent diminution in its toxicity

"Tetanus anti-toxin does not pass to the central nervous system either by way of the blood vessels, axis cylinders, or neural lymphatic channels. It also cannot pass from the cerebrospinal fluid when inoculated intra-theically into the substance of the cord. The antitoxin simply acts by combining with the circulating toxin, and that at the seat of production, and prevents it from reaching the central nervous system. The toxin already in this position is unaffected." Thus, the use of antitoxin in man, if not wholly preventive, often permits the development of localized tetanus⁵⁴

51 Bolton, B. M., and Fisch, C. *Tr. A. Am. Phys.* **17** 462, 1902

52 Bailly, G. *Bull. Soc. Med. Vet.*, 1925, abstr., *Bull. de l'Inst. Pasteur* **24** 31, 1926

53 Teale, F. H., and Embleton, D. *J. Path. & Bact.* **23** 50, 1919

54 Burrows, H. *Lancet* **1** 139, 1917

After the toxin reaches the spinal cord its further diffusion according to Ponomareff⁵⁵ may proceed either by the nerve substance or by the cephalo-arachnoid fluid, diffusion by the latter vehicle supposedly accounting for the rapid development of generalized symptoms of tetanus following localized tetanus in some cases. Ponomareff supported this view by an ingenious experiment in dogs in which the sub-arachnoid space in the brain was separated from that of the cord by a muscular ring reducing the freedom of circulation of the fluid. Animals so treated and inoculated in one of the hind legs always developed symptoms of generalized tetanus from ten to thirty hours later than did untreated controls similarly inoculated. Similarly in normal inoculated dogs in which the anterior movement of cephalo-arachnoid fluid from the cord to the brain was accelerated by repeated withdrawal of fluid from the brain the symptoms of generalized tetanus appeared from eight to fifteen hours earlier than in the untreated controls.

LESIONS IN TETANUS

The literature dealing with this phase of the subject is scanty and somewhat conflicting. In natural tetanus the primary wound may vary from a bee sting to a comminuted fracture with deep lacerations. The resulting secondary infection may be so slight as to involve almost no marked local reaction or it may be so severe because of secondary infections as to result in gaseous gangrene. In the so-called "idiopathic" tetanus it may be impossible to detect the primary lesion, particularly if it is hidden in the viscera, and "there are no clinical features of a wound pathognomonic of tetanus infection."

The marked antemortem rigor of tetanus disappears at once on death and sometimes even a few moments before death, on the other hand there is some evidence that the usual postmortem rigor develops more rapidly following tetanus possibly due to the saturation of the muscles with the products of their extreme activity, but of course, such rigor has no significance in the diagnosis of tetanus at autopsy.

When one performs an autopsy on guinea-pigs dead of experimental tetanus one rarely sees any macroscopic lesion except a slight congestion at the site of inoculation in material from which it is usually impossible to stain micro-organisms or to recover cultures, the viscera are practically always normal to the naked eye, with the exception of slight pulmonary congestion in occasional instances.

Stangl⁵⁶ found that guinea-pigs into which pure cultures of *B. tetani* had been injected in sufficient quantity to produce symptoms within twelve hours revealed at that time an intense cellular invasion

⁵⁵ Ponomareff A W. Compt rend Soc de biol **97** 503 1927

⁵⁶ Stangl F H. J Infect Dis **31** 22 1922

which sharply defined the affected area, but which never led to definite necrosis or abscess formation, although from 80 to 90 per cent of the cells were polymorphonuclear leukocytes, the remainder being mononuclear leukocytes and large mononuclear wandering cells. Stangl noted that the capillaries were engorged and the endothelial cells enlarged in the area surrounding the point of inoculation. Most of the bacilli were observed in the spaces between the leukocytes and the fixed cells, but a few were found within the leukocytes. At this stage there was neither hyaline nor waxy change in the muscle fibers, but the nuclei of the sarcolemma were swollen.

In older lesions, the polymorphonuclear leukocytes became less numerous while lymphocytes and mononuclear wandering cells increased to one third or one half of the cells present. Still later (from five to six days) large fibroblasts and giant cells were present, suggesting a reparative phase of the reaction.

Stangl also noted disappearance of the striations in the muscles, granular disintegration of the nuclei and a well defined waxy degeneration. Microscopic changes similar to those observed in guinea-pigs were also seen in a local lesion studied post mortem in a case in man. It would be interesting to confirm these results and compare the action of toxin with that of whole cultures.

Marinesco⁵⁷ found hemorrhages in the gray matter of the cords of guinea-pigs dead after an injection of tetanus toxin. The ganglion cells had also become smaller and more fusiform. The cell plasma was more than ordinarily granular and failed to show the usual differentiation on staining. When the convulsions had lasted for some time, the nucleus was said "to be ill defined and to stain more intensely than usual," which sounds like a contradictory statement. The medullated nerve fibers were also found to be degenerated in such cases. Hunter⁵⁸ found similar hyperemic changes in the cords of two human victims, with altered ganglion cells, but failed to find them in a third case, undoubtedly tetanus, since the bacillus was cultivated from the wound. Hunter considered the hyperemia of the cord to be a nonspecific action of the toxin.

Goldscheider and Flatau⁵⁹ observed certain characteristic changes in the motor cells of the anterior horns in experimentally tetanized rabbits depending in the order of their development on the concentration of toxin injected and the duration of the disease. These were best displayed by Nissl's stain and consisted primarily in an enlargement of the

57 Marinesco, G. *Gazettes méd.*, Paris, July 11, 1896, quoted by Hunter (footnote 58).

58 Hunter, W. K. *Brit. M. J.* 2: 333, 1927.

59 Goldscheider, A., and Flatau, E. *Fortschr. d. Med.* 1897-1898, quoted by Moschcowitz (footnote 64).

nuclei, which at the same time became less distinct, followed by an enlargement and disintegration of Nissl's cell and granules, and an enlargement of the whole cell. Therapeutic use of antitoxin had a distinct retarding influence on these changes. They subsequently verified these observations in the spinal cord of a human victim of tetanus, and essentially similar results are said to have been obtained by Matthes,⁶⁰ Westphal,⁶¹ Goebel⁶² and Tauber⁶³. Moschcowitz⁶⁴ considered that these changes are "characteristic of tetanus and are constantly found." One may well agree with him that "our present knowledge of the pathogenesis of tetanus points with great probability to the anterior horns of the spinal cord as the primary seat of origin for the tetanic contraction." It is clear from this why the period of incubation in tetanus is shorter and death comes sooner when the path from lesion to cord is short, as Kairinkschtis⁶⁵ and others have noted.

Nelson⁶⁶ recently observed in a single case that the changes usually observed in the cells of the anterior roots of the cord may also be seen in those of the posterior roots, particularly at the level of the fifth lumbar segment, and suggested, on the one hand, that the toxin might be transmitted by the nerve fibers of the sensory root as well as by those of the motor root, or, on the other, that diffusion of the toxin might proceed by the perineural lymphatics outward from the cord so as to injure the cells of the posterior root ganglion, in which case the maximal degree of injury in the posterior root ganglion of the fifth lumbar segment might be correlated with a maximal concentration of toxin at the level at which the toxin entered the cord.

60 Matthes, P. *Deutsche Ztschr f Nervenhe*, 1898, quoted by Moschcowitz (footnote 64)

61 Westphal, A. *Fortschr d Med*, 1898, quoted by Moschcowitz (footnote 64)

62 Goebel, W. *Monatschr f Psychiat u Neurol*, 1898, quoted by Moschcowitz (footnote 64)

63 Tauber, A. S. *Wien klin Wchnschr*, 1898, quoted by Moschcowitz (footnote 64)

64 Moschcowitz, A. V. *Ann Surg* **32** 219, 1900

65 Kairinkschtis, W. *Ztschr f Hyg* **95** 220, 1922

66 Nelson, S. H. *Lancet* **2** 852, 1926

Notes and News

University News, Promotions, Resignations, Appointments, Deaths — Thorburn Brailsford Robertson, professor of biochemistry and general physiology in the University of Adelaide, has died of pneumonia at the age of 45

M Fernan-Nunez, a graduate of the University of Madrid in 1925, has been appointed director of the department of pathology and bacteriology in Marquette University, Milwaukee

George W Bachman, formerly of the school of hygiene and public health of Johns Hopkins University, is now professor of parasitology in Columbia University, with duties in the school of tropical medicine, University of Porto Rico

Stuart Graves, dean and professor of pathology in the school of medicine of Alabama University, has resigned as acting state health officer

David R Briggs has been appointed as assistant professor of chemistry in the department of pathology of the University of Chicago

I S Falk has resigned as professor in the department of hygiene and bacteriology, University of Chicago

In the school of medicine of the University of Illinois, George Milles and Louis Parmacek have been appointed instructors in the department of pathology and bacteriology, and A J Nedzel instructor in the department of bacteriology and preventive medicine

Robert Muir, professor of pathology in the University of Glasgow, has been awarded a Royal medal by the Royal Society of London in recognition of his work in immunology and experimental pathology

A department of medical and surgical research has been established in the Ohio State University, with Charles A Doan of the Rockefeller Institute for Medical Research as chairman

Robert W Lamson has been appointed associate professor of bacteriology and immunology in the University of Southern California

David H Kling has accepted a Frederick Brown fellowship in orthopedic research at the Hospital for Joint Diseases in New York

Milton G Bohrod has been appointed pathologist to the Decatur and Macon County Hospital, Decatur, Ill

William K Hueper, associate professor of pathology in Loyola University and pathologist to Mercy Hospital, Chicago, has been appointed pathologist to the Oncologic Hospital in Philadelphia

William Royal Stokes, professor of bacteriology, University of Maryland, and city bacteriologist, Baltimore, has died from parrot fever contracted from handling infected parrots, at the age of 60 years

Cancer Research —The University of California now has an endowment of \$200,000 for research in cancer and allied subjects

The fund for cancer research at the graduate school of medicine of the University of Pennsylvania has received \$210,000 from an unnamed donor. The director of the fund is Ellice McDonald, who is also chairman of a board of directors of research. A central laboratory has been established, with departments for tissue culture, for experimental cancer in animals, and for the study of problems in radiation (in cooperation with the Bartol Research Foundation). The plans also include the development of a complete anticancer center at the American Oncologic Hospital, and of research on the biochemistry and immunology of cancer at the Philadelphia General Hospital. Grants have been made for work on the metabolism of cells (W D Bancroft, Cornell University), on the fixation of pathologic material (Henry J Fry, New York University), on the sensitization of cells to fluorescent substances and roentgen rays (Eric Ponder, New York University), and on the quantitative spectrographic estimation of substances in biologic material (Andrew Dingwall, Columbia University)

University of Cambridge Studentships—1 Gwyneth Pretty Studentship, the holder of which shall devote himself to original research in the etiology, pathology and treatment of disease with particular but not exclusive reference to those diseases which cripple or disable in childhood or early life is of the annual value of £200 and is tenable for three years

2 John Lucas Walker Studentship, the holder of which shall devote himself to original research in pathology, is of the annual value of £300 and is tenable for three years

Applications for these studentships accompanied by copies of papers containing published work, testimonials and references, should be sent before July 1, 1930, to Prof H R Dean, Department of Pathology, University of Cambridge to whom also applications for further information regarding the studentships may be addressed

The International Association for Geographic Pathology—In 1928, Max Askanazy presented a plan for a coordinated study of pathologic conditions which show geographic variations and for the organization of an international association for that purpose. The project was favorably received by European pathologists, and Max Askanazy, Ludwig Aschoff, Gustav Roussey and Joselin de Jong constituted themselves a voluntary bureau to organize the proposed association. One pathologist from each of different countries was invited to represent his country on an international commission and to organize in his country a national committee to carry on such investigations and collect such data as may be appropriate to the problems under consideration.

Representatives from several countries held an informal meeting in Vienna, in April 1929 and arranged plans for the ensuing year. Cirrhosis of the liver was selected as the first subject for a geographic study. The bureau has announced that the first formal meeting of the commissioners will be held at Geneva in the late summer of 1931. At that time the report on cirrhosis will be presented and the formal organization of the association completed.

National committees have now been formed in the following countries: Argentine, Austria, Baltic Provinces, Belgium, Brazil, Bulgaria, Canada, Central America, Czechoslovakia, Denmark, England, Finland, France, Germany, Greece, Holland, Hungary, Italy, Japan, Jugoslavia, Lettland, Lithuania, Lower India, Norway, Poland, Portugal, Roumania, Russia, South Africa, Spain, Sweden, Switzerland, Turkey and the United States. V H Moon, of Philadelphia, was chosen by the bureau as the representative for the United States. D J Davis of Chicago, Wiley D Forbus, of Baltimore, Ernest M Hall, of Los Angeles, Howard T Karsner, of Cleveland, Leo Loeb, of St Louis, David Marine, of New York, Frank L Menne, Portland, V H Moon, of Philadelphia and Fred-eric Parker Jr, of Boston constitute the national committee for the United States.

Status of British Hospital Pathologists—According to the *British Medical Journal*, the following recommendations concerning hospital pathologists have been submitted for inclusion in the Hospital Policy of the British Medical Association. That every hospital having at least 200 beds should maintain its own pathologic department. When several hospitals exist in one area it may be sufficient to maintain between them a common department, that the department should be under the direction of a fully qualified medical practitioner who has had special training in pathology, that the pathologist in charge should be regarded as having a status similar to that of other members of the visiting staff, that the hospital work should be the first care of the pathologist, that in return for the performance of the hospital work the hospital should (a) pay a fixed salary to the pathologist in charge of the department, and (b) bear the full cost of the maintenance of the department and of such a staff, qualified and unqualified, as may be necessary for the efficient work of the hospital, that in suitable circumstances the pathologist in charge be permitted private practice as a consulting pathologist, and allowed to do private laboratory work in the hospital by agreement with the governing body.

Death of Benjamin Roman—Benjamin Roman, pathologist to the Buffalo General Hospital and research professor of pathology in the University of Buffalo, died of pneumonia, at the age of 53. A few days after his death his widow died, also of pneumonia. Dr. Roman was born in Lithuania but was educated in this country and graduated from Cornell University Medical College in 1903. He spent many years in Europe and studied pathologic anatomy in Vienna and then at the German University in Prague, where he was assistant for several years until the United States entered the War. In 1919 he was chief pathologist to the American Zionist Unit in Palestine, and in 1921 he came to Buffalo. He was an accomplished pathologic anatomist and published results of thorough studies on the portal of entry of the tubercle bacillus, on diseases of the hemopoietic organs, on canine distemper and on other topics. In Buffalo he took an active interest in the *Bulletin of the Buffalo General Hospital*, and he was particularly influential in the staff conferences.



BENJAMIN ROMAN, M.D.

DOCTORATES IN HUMAN AND ANIMAL BACTERIOLOGY
AND PATHOLOGY CONFERRED BY AMERICAN
UNIVERSITIES, 1928-1929

Callie Hull and Clarence J. West, Research Information Service,
National Research Council, Washington, D. C.

California Oscar Brown Williams, "Studies on the Heat Resistance of Bacterial Spores"

Chicago Janet MacFarlane Bourn, "Incidence of Pfeiffer's Bacillus in Throats During Epidemic and Interepidemic Periods in Chicago" Graeme Alexander Canning, "Preciptin Reactions with Various Tissues of *Ascaris lumbricoides* and Related Helminths" George Wilham Stuppy, "The Production and Prevention of Pneumonia and Other Pneumococcus Infections. Experiments on the Rabbit and on Monkeys (*Macacus rhesus* and *Cebus capucinus*)" Adah Elizabeth Verder, "Effect of Diets Deficient in Vitamin A or B on Resistance to Paratyphoid-Enteritidis Organisms"

Columbia Richard Warner Linton, "Mobilization and Transfer of Clasmato-cytes" Gonzalo Palacios de Borao, "An Epidemiological Study of Leprosy in Porto Rico with Special Reference to Topographic and Climatic Factors"

Cornell Georges Abdallah Knaysi, "The Cytology and Microchemistry of Mycobacterium Tuberculosis" Ruth Alice Boak, "The Etiology and Diagnosis of Undulant Fever in the United States"

Kansas Louis H Bally, "Studies in Experimental Anaphylaxis" Clara Nigg, "Studies on Isohemagglutination"

Minnesota Hilding Cornelius Anderson, "Studies of the Effects of Surgical Reduction of the Renal Tissue" Leone McGregor, "The Finer Histology of the Normal Glomerulus and the Changes that Occur in Glomerulonephritis"

New York James Franklin Yeager, Jr, "Studies in Hemolysis"

Northwestern William Walter Brandes, "Studies on the Effect of Mechanical Constriction of the Hepatic Veins with Special Reference to the Coagulation of Blood"

Pennsylvania Mary Jardine Evans, "A Study on *Hemophilus influenzae*"

Stanford Paul Jay Beard, "Studies on the Adaptation of the Bacteriophage"

Wisconsin Frances Elizabeth Holford, "The Placental Transmission of Foreign Protein in Rabbits"

Yale Frederick William Fabian "The Influence of Cations upon Bacterial Viability at Various Hydrogen Ion Concentrations" Edward Winfield Morrison, "Selected Properties and Responses of Bacterial Spores"

Obituary

RICHARD MILLS PEARCE, JR., M D

1874-1930

Richard Mills Pearce, Jr., was born of American parents in Montreal, Canada, March 3, 1874. His family moved to Boston, where he completed his preliminary education at the Boston Latin School. He was graduated from the Harvard Medical School in 1897 with the degree M D. The honorary degree Sc D was conferred on him by Lafayette College of Easton, Pa., in 1915. From 1896 to 1899, he was with Mallory at the Boston City Hospital and was then with Councilman at the Harvard Medical School for one year, after which he headed the remarkable group of young men appointed by Flexner when the latter occupied the chair of pathology at the University of Pennsylvania. During part of 1901 and 1902, he worked at Leipzig with Marchand, and in 1903 he became professor of pathology and bacteriology at Albany Medical College, director of the Bender Hygienic Laboratory and director of the Bureau of Pathology and Bacteriology of the New York State Department of Health. In 1908, he accepted the chair of pathology, originally established by Welch, at University and Bellevue Hospital Medical College, New York. In 1910, he was called to the University of Pennsylvania for the newly created chair of research medicine which was later given the name of the man in whose honor it was endowed, John Herr Musser. Ricketts was appointed professor of pathology at about the same time, but died a martyr before he could assume his new duties. At this juncture, Pearce consented to occupy both chairs until a new professor of pathology could be appointed. At the end of a year, Allen J. Smith returned to the chair of pathology, which he had relinquished to establish a department of tropical medicine. In the later years of Pearce's incumbency in the chair of research medicine he made numerous surveys of foreign medical education for the Rockefeller Foundation and in 1920 he became director of the Division of Medical Education of the Rockefeller Foundation. During the Great War, he was in charge of the correlation of medical research in the Council of National Defense, with the rank of major, M C, U S Army, and became the first chairman of the Division of Medical Sciences of the National Research Council.

Pearce was a member of many of the important medical and biological societies. He was president of the American Association of



Marceau

RICHARD MILLS PEARCE, JR, M D
1874-1930

Pathologists and Bacteriologists in 1912 and of the American and Canadian Section of the International Association of Medical Museums in 1914. He was the leader of a group which established the American Society for Experimental Pathology in 1914 and was its first president. In 1915, he was a vice-president of the American Association for the Advancement of Science. In 1904, only seven years after graduation, he was elected a member of the Association of American Physicians. In 1909, he delivered a Harvey lecture, "Problems of Experimental Nephritis," and in 1920 was Hitchcock lecturer at California, where he delivered a remarkable series of five lectures on the subject "Research in Medicine."

Sturdy and robust in appearance and with great physical energy, he was nevertheless handicapped by a thrombosis of the femoral vein incident to typhoid fever. In 1926, he had the first symptoms of cardiac disease, and in the early autumn of 1929 he had symptoms and signs of myocardial infarction. His abrupt death on Feb. 16, 1930, was due to coronary disease and extensive infarction.

Pearce's research work was always based on concrete problems from the period of his early work on pneumonia and diphtheria, through that on necrosis of the liver, renal disease and function of the spleen. To the solution of these problems he brought an imagination sane and well controlled, but always constructive. The attack might be anatomic, histologic, physiologic, chemical, bacteriologic, immunologic or clinical or any possible combination of these, but methods were no barrier to the exploration, for Pearce had a comprehensive grasp of them all. If technic was to be learned, he learned it, or if he delegated it to an associate, he supervised and criticized the work so that he always shared the responsibility.

Extraordinary devotion to the enlargement of the field of knowledge by research never interfered with his activities in teaching. On the contrary, it appeared to bring him to his classes with an ever refreshed enthusiasm. His lectures were models of order and clarity, and the brevity with which he presented a full discussion of a given topic was unparalleled. He introduced to this country the utilization of the methods and results of experimentation for large classes of students. He had a genuine interest in all his students, but gave particular attention to the welfare of the gifted ones. At Pennsylvania this was shown in a material way by the establishment of a chapter of a national medical fraternity and a chapter of Alpha Omega Alpha honorary medical fraternity. His pupils occupy important posts in universities and hospitals throughout this country, and it is noteworthy that two chairs at the University of Pennsylvania are now occupied by men who received much of their training and stimulus from Pearce.

Pearce's studies of the philosophy of education as applied to medicine resulted in numerous important publications on the subject. With a background of history and philosophy, he brought to these problems scrupulous analysis and thoughtful consideration, which resulted in clear, logical and convincing documents. Their value was reflected not only in his university work, but more broadly in the advice which he was able to give and the projects in the inauguration of which he played a part as an officer of the Rockefeller Foundation.

A natural reserve of manner never submerged his quiet geniality. His broad vision, reinforced by a ready sense of humor, and a reasoning tolerance overbalancing an impatience at waste or indirection brought a convincing sympathy to his consideration of problems and projects. His straightforward arrival at conclusions led to statements at once brief, clear and indubitably sincere. In his publications, he showed in the more general articles a fluent and attractive style and in his scientific communications an astonishing clarity and conciseness. In both, he showed his appreciation of the precise use of words and the refined beauties of the English language. Fond of the open air and the glories of nature, devoted to family and home, his life was well balanced. The strength and fineness of his character were reflected in his entire mode of living, especially in the genuine joy of his work. Duty and service were his doctrine, and he himself exemplified the precept which he quoted from Pasteur, "Work can be made into a pleasure and *alone* is profitable to a man to his country to the world."

H T K

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE VELOCITY OF THE BLOOD FLOW IN HEALTH AND DISEASE S WEISS,
G P ROBB and H L BLUMGART, Am Heart J 4 664, 1929

A technic is described by which the velocity of the blood flow may be measured by estimating the difference between the reaction times of histamine at the site of intravenous injection and in the vessels of the face and brain. A markedly prolonged circulation time was always associated with severe circulatory failure, but the reverse was not always true. The velocity of the blood flow was studied in a considerable variety of pathologic conditions and was found to be an important diagnostic aid in differentiating certain diseases associated with dyspnea and edema.

PEARL ZEEK

THE INFLUENCE OF CERTAIN IRON OXIDES ON THE BLOOD C A DOAN,
F R SABIN and C E FORKNER, Am J M Sc 117 201, 1929

Certain iron compounds (Fe_3O_4 and $\text{Fe}_2\text{O}_3 \times \text{H}_2\text{O}$) administered to normal rabbits and to those suffering from anemia after hemorrhage produce definite depression of hemopoiesis and are probably disadvantageous therapeutically in clinical cases of secondary anemia.

PEARL ZEEK

THE EFFECT OF COMBINED POTASSIUM IODIDE AND THYROID SUBSTANCE UPON
THE THYROID GLAND S H GRAY and J RABINOVITCH, Am J Path 5
485, 1929

Feeding of potassium iodide to normal guinea-pigs stimulates the thyroid gland whereas feeding of thyroid substance produces the opposite effect. In feeding potassium iodide and thyroid concomitantly, the effect of the former is evidenced by the increased size of the epithelium, and the effect of the thyroid substance is manifested by the hardness of the colloid and the diminished number of mitoses. Preliminary feeding of potassium iodide interferes only slightly with the subsequent depressive action of thyroid substance, and similarly a preliminary feeding of thyroid substance affects only to a small extent the subsequent stimulative effects produced by the feeding of potassium iodide.

AUTHORS' SUMMARY

THE INFLUENCE OF SUPRARENAL CORTEX AND MEDULLA ON THE GROWTH AND
MATURITY OF YOUNG CHICKS A G EATON, W M INSKO, G P THOMP-
SON and F E CHIDESTER, Am J Physiol 88 187, 1929

In groups of young chicks which were fed with desiccated suprarenal cortex and medulla, respectively, in addition to standard rations, it was found that with the feeding of medulla, initial growth rate was unchanged for the first three weeks after which time the chicks showed less rapid growth. Those fed with cortex showed an early marked retardation of growth, lasting for about eight weeks, but at the end of that time they began to grow more rapidly, and quickly gained until at the end of eleven weeks' observation they almost equalled the controls. Using testicular weight as a criterion, males receiving desiccated cortex matured more rapidly, while those receiving medulla were less mature than control animals.

H E EGGERS

THE INFLUENCE OF DESICCATED SUPRARENAL CORTEX AND MEDULLA ON THE GROWTH AND MATURITY OF YOUNG RATS F E CHIDESTER, A G EATON and G P THOMPSON, *Am J Physiol* 88 191, 1929

With young rats fed on desiccated suprarenal cortex or medulla in addition to standard diet, it was found that growth was retarded by both, the greater retardation occurring with the cortex. Young females fed with the cortex reached sexual maturity sooner than did the controls or the animals fed on medulla. As males were not tested independently with older females, it was not determined whether these reached sexual maturity before the corresponding females.

H E EGGERS

THE PERMEABILITY OF THE PLACENTA OF THE RAT TO GLYCERINE, ALANINE AND UREA J M LUCK and E T ENGLR, *Am J Physiol* 88 230, 1929

Following the subcutaneous injection of glycerin, alanine and urea into pregnant rats, subsequent determinations of these substances showed that the rates of increase of these in the maternal muscle and in the whole fetus were very similar, indicating not only that the placenta is very permeable for these substances, but that the mechanism of absorption by these tissues from the respective plasmas is apparently identical. Very rapid absorption was found of the amino-acids by the liver, apparently with a mechanism of absorption quite different from that operating in muscle.

H E EGGERS

PHYSIOLOGY OF THE CORPUS LUTEUM W M ALLEN and G W CORNER, *Am J Physiol* 88 340, 1929

Rabbits were deprived of both ovaries in the eighteenth hour of pregnancy, and the progestational proliferation of the endometrium was maintained by the daily administration of corpus luteum extracts, in these circumstances the embryos survived and grew normally, with normal implantation. In the absence of this induced progestational proliferation, the embryos did not survive beyond the fourth day. These observations are interpreted as certain evidence that the corpus luteum is an organ of internal secretion, having for one of its functions the production of a hormone which induces the special state of the uterine mucosa without which the free blastocytes lack essential protection or nourishment.

H E EGGERS

OBSERVATIONS ON THE FUNCTION OF THE GALL BLADDER B HALPERT and M T HANKE, *Am J Physiol* 88 351, 1929

Following the oral or intravenous administration of methylene blue (methylthionine chloride, U S P), the dye appears in the bile and the authors describe a colorimetric method for its measurement here. The pigment appears promptly, within a few minutes after its intravenous injection. The quantity in the bile rises sharply to its maximum in about one hour, after which it declines gradually. In bile removed from the gallbladder six hours after injection, there is from two to twenty-two times as much of the dye as is found in corresponding samples from the common duct. At times the concentration of methylene blue in the gallbladder is considerably greater than is ever found in the bile leaving the liver. Since the dye is not excreted by the gallbladder, its increased concentration there is explained on the basis of a slower rate of absorption there than that of the bile. Also, the writers believe that ordinarily bile does not leave the gallbladder via the cystic duct.

H E EGGERS

DIABETES INSIPIDUS—THE DIURETIC SUBSTANCE H BOURQUIN, *Am J Physiol* 88 519, 1929

A diuretic substance has been demonstrated in dogs with experimental diabetes insipidus, which is not found in the urine of normal dogs. Such a substance has also been demonstrated in extracts of large amounts of the mammillary bodies and thal-

amus of the brains of normal animals, and is not found in any appreciable quantity in other parts of the brain. Both diuretic substances are destroyed by strong alkaline solutions at room temperature, are destroyed by ashing, are not dissolved by ether, acetone or 95 per cent alcohol, are precipitated by barium hydroxide from somewhat alkaline solution and are not precipitated by phosphotungstic acid. From their similarities in these respects, it may be inferred that they are identical.

H. E. EGGERS

HYPERINSULINISM. REPORT OF TWO CASES. FRANK N. ALIAN, Arch Int Med 44 65, 1929

Hyperinsulinism due to overproduction of insulin from a tumor of the islands of the pancreas is now established as a disease entity. It is probable that hyperinsulinism may also be due to a functional disturbance of the pancreas. The differential diagnosis of hypoglycemia due to hyperinsulinism and hypoglycemia due to selective hepatic insufficiency is a difficult clinical problem. Two criteria may have value in differentiation: the effect of epinephrine hydrochloride and solution of pituitary, and the amount of sugar required to maintain the blood sugar level. When the hypoglycemic tendency is so strong that the patient is incapacitated, surgical treatment appears to promise relief. Three cases are described in which there was a constant tendency to severe hypoglycemia attributed to hyperinsulinism. In case 1, there was a carcinoma of the islands of Langerhans. In case 2, surgical exploration revealed a normal appearing pancreas. Resection of a part of the pancreas was followed by considerable relief. In case 3, in which medical treatment alone was given, the patient is still under observation.

AUTHOR'S SUMMARY

TOXIC CIRRHOSIS OF LIVER DUE TO CINCHOPHEN. HERBERT S. REICHLER, Arch Int Med 44 281, 1929

Forty-seven cases of cinchophen toxicosis have been published. Ten deaths have resulted. In all cases there is evidence of serious damage of the liver. Every patient who receives cinchophen should be observed for gastro-intestinal symptoms, rashes or icterus, and the occurrence of such symptoms should be the immediate indication for stopping the use of the drug. The therapeutic use of cinchophen may well be reevaluated in reference to its harmful properties.

AUTHOR'S SUMMARY

CONSTITUTIONAL VARIATION AND SUSCEPTIBILITY TO DISEASE. WADE H. BROWN, Arch Int Med 44 625, 1929

So far as they go, my experiments not only are in harmony with known facts concerning human constitution and susceptibility to disease, but they enable one to state some of the general principles of the constitutional concept in simple terms of present knowledge and to visualize conditions which may influence susceptibility to disease. Constitution thus becomes a concrete reality which lends itself to measurement and test in accordance with the demands of modern science. The elementary conception of constitutional variation and its relation to disease, which I have attempted to outline, involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and tissues, and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from one another in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic microorganisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by changing conditions of life and that these variations in organic constitution are accompanied by variations in chemical constitution, all of which may well be confined within the

usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity. Changing conditions of life affect individuals and groups, but as individuals differ in respect of their inherent constitutional equipment, they differ also in their reaction to influences of all kinds. Some are capable of immediate and complete adjustment and others are slow to respond or are incapable of adjustment, so that when the members of a group are subjected to a change in the conditions of life or are exposed to infection under favorable or unfavorable conditions, the response obtained varies according to the capacities of the individual. Hence, even now, there is some understanding of how and why one person differs from another in respect to the general property of susceptibility to disease and why it is that the susceptibility of persons and of populations is not fixed but varies from time to time, independent of any immunity that may be acquired through previous exposure to a given disease. When one is able to base all experiments on material of known genetic constitution and thus link together the two factors of heredity and environment, one will be in a position to gain a much clearer understanding of these intricate problems.

AUTHOR'S SUMMARY

THE EFFECT OF MECHANICAL CONSTRICTION OF THE HEPATIC VEINS WITH SPECIAL REFERENCE TO THE COAGULATION OF BLOOD. W. W. BRANDES, *Arch. Int. Med.* **44**: 676, 1929.

A method of mechanically constricting the hepatic veins in the dog has been described. This procedure permits a study of changes occurring in the blood following removal of the liver from and its return to, the circulation. Following this constriction there is a precipitate fall in blood pressure of from 40 to 60 mm. of mercury, a level which is then maintained reasonably constant for twenty minutes or more. A decrease in the concentration of the blood (an average of 11 per cent in six dogs) with a gradual increase in concentration occurs until, at the end of fifteen minutes, the normal value is approximately reached. A rapid decrease in the blood sugar (average of 42 per cent) is obtained during constriction for fifteen minutes with a rapid rise after release. A definite decrease in coagulation time of from 25 to 50 per cent is observed during constriction followed by an increase on release. There was a slight decrease of fibrinogen (11 per cent) during constriction and a definite increase of 25 per cent or more on release of constriction. The platelets were slightly decreased (15 per cent) during constriction with slight change on release. Changes in blood calcium can be accounted for by dilution. The experimental results reported indicate that the chief factors, the interaction of which is concerned in the changes in coagulation time during and after constriction of the hepatic veins, are alterations in antithrombin (heparin) content, increase in the hydrogen ion concentration, and numerical changes in platelets.

AUTHOR'S SUMMARY

DIABETES IN TWINS. W. STANLEY CURTIS, *J. A. M. A.* **92**: 952, 1929.

Only seven instances of diabetes in twins are on record. To these six are now added, making a total of thirteen. The existence of diabetes in twins in some cases almost simultaneously points to an hereditary background and offers a good field for the investigation of diabetes as a problem in heredity. When diabetes develops in a twin one should consider the other potentially diabetic, particularly if the two are homologous, and any undue strain on the carbohydrate metabolism should be guarded against.

The recognition of eight twins (four sets) with diabetes in a series of 6,000 diabetic patients, when compared with the estimated number of twins in such a group, suggests a larger portion of diabetes in twins (1 to 9) than is the case in

single individuals. It is to be hoped that others who have had similar cases will report them, in order to confirm or disprove these meager data.

AUTHOR'S SUMMARY

CELL PROLIFERATION RESPONSE TO SULFHYDRYL IN MAMMALS. T. S. HAMMETT and S. P. REIMANN, *J. Exper. Med.* **50** 445, 1929.

These experiments establish the fact that the sulfhydryl group is stimulative of cell proliferation in mammals as in lower organisms. The fact that the stimulation is exhibited in such a wide diversity of species including both plants and animals is justification for the belief that it is the expression of a fundamental biologic phenomenon.

AUTHORS' SUMMARY

STUDIES OF TISSUE MAINTENANCE. PERSISTING BLOODLESSNESS AFTER FUNCTIONAL ISCHEMIA. H. P. GILDING and PEYTON ROUS, *J. Exper. Med.* **50** 471, 1929.

In regions of the skin which have been bloodless for some time, as a result of the functional readjustments following a reduction of the blood bulk, the ischemia persists long after the blood volume has been restored and the systemic blood pressure has mounted to the initial level or a higher one. The significance of this is briefly discussed.

AUTHORS' SUMMARY

THE FINAL RESPONSE OF THE SNAIL CUTANEOUS VESSELS. PEYTON ROUS and H. P. GILDING, *J. Exper. Med.* **50** 489, 1929.

A study of the blanchings (Bier's spots) which develop in human skin deprived of circulation has proved them referable to the same general causes that lead to ischemic patching of the skin of animals, and that they are conditioned by the same factors. Both are expressions of a secondary contraction of vessels that have become hyperirritable owing to an inadequate circulation. The contraction is favored by emptying the vessels, but it occurs pronouncedly even when there is a trickle through them of arterial blood. In the case of man the contractile impulse is sometimes so great as to overcome the maximum pressure that the vessels will support. The significance of the observations is discussed.

AUTHORS' SUMMARY

THE LIVER AS THE SOURCE OF FIBRINOGEN. D. R. DRURY and PHILIP D. McMASTER, *J. Exper. Med.* **50** 569, 1929.

In hepatectomized rabbits a progressive decrease in blood fibrinogen occurs. Partial defibrination in the liverless rabbit invariably results in a progressive decrease in blood fibrinogen preceded by a temporary and slight rise. No evidence has been secured of fibrinogen regeneration in the absence of the liver. From this it follows that the liver is the essential source of fibrinogen and in all probability the sole one.

AUTHORS' SUMMARY

A MECHANISM OF CONSERVATION IN THE KIDNEYS OF THE WINTER FROG. JEAN OLIVER and ESHREF SHAFAY, *J. Exper. Med.* **50** 601, 1929.

A method of conservation has been demonstrated in the kidneys of winter frogs. The mechanism of this conservation is an increase in the absorptive function and a decrease in the excretory activity of the tubular epithelium. The excessive absorptive process may be depressed by various means. Such a depression in the tubular activity is followed by large increases in the rate of excretion of water, salts and, if present in the urine, phenolsulphonphthalein. Further evidence is thus obtained which supports the theory that phenolsulphonphthalein is excreted chiefly through the glomeruli.

AUTHORS' SUMMARY

TESTS WITH VARIOUS FOODS IN SPRUE CHARLES WEISS and O COSTA
MANDRY, J Immunol **16** 283, 1929

An investigation was made to determine whether the untoward gastro-intestinal reactions observed in patients with sprue (diarrhea, tympanites, flatulence, etc) after eating certain types of food might be of the nature of specific hypersensitiveness. A careful survey was made of the foods commonly eaten by the people of Porto Rico and representative types were selected for cutaneous tests. These include proteins prepared from rice, beans, pork, cod-fish, coconut, etc., sugars (saccharose and fructose), fats and oils (lard, butter, etc.), starches prepared from rice, potatoes, beans, etc., and local spices and coffee. The results were clearly negative and indicate that the untoward digestive symptoms in patients with sprue are not due to any specific sensitization to any food products.

AUTHORS' SUMMARY

THE ACTION OF AUSTRALIAN SNAKE VENOMS ON PLAIN MUSCLE C H
KELLAWAY, Brit J Exper Path **10** 281, 1929

All the Australian elapine venoms tested have a stimulant action on isolated plain muscle. The type of action resembles the anaphylactic reaction of the isolated plain muscle of the guinea-pig in its latent period, and in the case with which the muscle is desensitized by the venoms of this group. The Australian venoms produce the reaction in varying concentrations. After reaction to one venom the plain muscle is insensitive to equivalent doses of the other venoms in the group. After desensitization the muscle does not recover its sensitiveness to snake venom, but its reactions to other stimuli are unimpaired. The plain muscle of guinea-pigs sensitized by the injection of egg albumin, after desensitization with snake venom retains unimpaired its sensitiveness to its specific anaphylactic antigen. After desensitization with egg albumin the muscle appears to be somewhat less sensitive to snake venom. Experiments with ergotoxin suggest that the effect of the venoms is a direct one on the plain muscle. The venoms cause contraction of the isolated uterus of the rat and the reaction of the plain muscle of the guinea-pig and the rabbit is therefore not due to the production of histamine, as this drug causes relaxation not contraction, in the uterus of the rat. The reaction differs from that caused by the toxin of *Vibrio septique*, and after desensitization with snake venoms a good reaction can be obtained with this toxin. The behavior of the only two other venoms tested (those of *Naja tripudians* and *Iperia russelli*) is quantitatively widely different from those of the Australian elapines. The stimulant principle in the Australian venoms is moderately thermostable, and is destroyed at from 92 to 94 C at about the same rate as the neurotoxic principle. Like the neurotoxic principle it appears to reside in the proteose fraction of the venom. At pressures of from 300 to 400 mm of mercury, and during a period of some hours, it only passes with difficulty through pyroxylin filters permeable to erythrocytes but not to egg albumin or hemoglobin. The stimulant principle is neutralized by antivenin, but the results obtained by titration, using the isolated plain muscle, are quantitatively widely different from those obtained by subcutaneous injection in guinea-pigs. Death-adder and tiger-snake antivenins give some protection against Australian venoms other than those against which they are prepared, and nonspecificity of the same order is observed in tests with the isolated plain muscle.

AUTHORS' SUMMARY

TETHELIN AS A TISSUE-CULTURE MEDIUM K C RICHARDSON and E S
HORNING, Australian J Exper Biol & M Sc **6** 137 1929

The growth-promoting qualities of tethelin have been confirmed in vitro. Cultures of intestinal epithelium from a seven-day embryo chicken in a medium of chick plasma, embryonic extract and tethelin or chick plasma and tethelin, give more extensive proliferation than do similar cultures in plasma and embryonic extract. Membrane formation taking place after twenty-eight hours' incubation in the former but not in the latter cultures.

AUTHORS' SUMMARY

EFFECT OF VITAL STORAGE ON OXYGEN CONSUMPTION OF THE KIDNEY
H OONK, Beitr z path Anat u z allg Path **79** 756, 1928

Gross, using the Warburg technic for determining cellular respiration, found that the presence of fat and glycogen in morphologic form within the liver cells of the mouse did not increase the oxygen consumption of such tissue, an indication that the fat and glycogen were inert in cellular metabolism. Oonk studied the effects of the vital storage of colloids on the cellular respiration of the kidney by the same technic. The acid vital dyes, trypan blue, lithium carmine and vital red, caused at first a slight increase in oxygen consumption, after which the oxygen intake returned to normal. The basic dye, neutral red, caused no change in tissue respiration. The early increase in oxygen consumption in the case of the acid dyes is due to the fact that the union of such dyes with the protoplasm in vital storage is an active metabolic process. After the dye has united with the protoplasm its presence has no effect on cellular metabolism. Because iron has been supposed to be important in intracellular metabolism, the effect of vital storage of saccharated iron oxide and of ferric citrate was also studied. Neither compound caused any change in tissue respiration, indicating that they are inert in intracellular metabolism, but indicating also that their presence does not depress cellular activity.

O T SCHULTZ

THE ABSORPTION AND EXCRETION OF SULPHUR BY THE SKIN R. STIGLER,
München med Wchnschr **76** 1795, 1929

Sulphur in ointments applied to the scalp is absorbed and to some extent is excreted by the skin of the entire body in the form of hydrogen sulphide.

AUTHOR'S SUMMARY

LYMPHATIC DRAINAGE OF CEREBROSPINAL SUBARACHNOID SPACE G IWANOW,
Ztschr f d ges exper Med **64** 356, 1929

Iwanow studied the course of lymphatic channels draining the subarachnoid space by following the paths of removal of india ink which had been injected subdurally into dogs. He claims that the particulate matter is removed fairly rapidly and in relatively large amounts from the cranial cavity by means of lymphatics which carry the material by rather direct routes to the cervical lymph nodes and to the lymphoid tissue aggregations of the mucosa of the upper air passages. The mucosal lymphoid follicles he considers important elements for the excretion of metabolic and other waste products derived from the brain. He disagrees with Weed, in that he ascribes only a minor role to the pacchionian granulations. These, according to Iwanow, remove the particulate matter used in his experiments only slowly and in small amounts. The paths of removal of the material from the spinal arachnoid space could be less clearly followed. Some of the material is undoubtedly carried upward to the cisterna at the base of the brain, its further fate being the same as that of the carbon particles injected directly into the cranial subdural space. Some of the material was found in the retro-peritoneal lymph nodes, in lymphatic channels of the mesentery and in Peyer's patches of the ileum. For the lymphoid tissue of the intestine he postulates an excretory function from the spinal subarachnoid space although he was unable to trace the continuous pathways.

O T SCHULTZ

EFFECT OF EXPERIMENTAL HYPERTHYROIDISM AND HYPOTHYROIDISM ON
GASTRIC HUNGER CONTRACTIONS A KRATNOFF, Ztschr f d ges exper
Med **64** 376 and 397, 1929

The frequent occurrence of gastro-intestinal disturbance in clinical hyperthyroidism led to the study of the effects of experimentally produced hyperthyroidism and hypothyroidism on the gastric hunger contractions of dogs. The

hyperthyroid state was brought about by a single 1 Gm dose of desiccated thyroid in twenty-four hours, by similar amounts of the same material daily over periods up to thirty days and by the intravenous injection of thyroxin. Gastric or duodenal contractions or both were studied by means of a balloon introduced through a permanent gastric or duodenal fistula. Desiccated thyroid caused an increase in the amplitude and frequency of the hunger contractions, led to the interpolation of contractions between the regular ones and increased the tonicity of the empty stomach. Thyroxin had the same effects, leading to the conclusion that the effects of desiccated thyroid were the specific ones of the contained thyroxin. In animals fed desiccated thyroid over a period of thirty days, cumulative effects were noted and alterations in the hunger contraction rhythm persisted for several months after administration of the material was stopped. Two of six dogs did not show the changes described. On the basis of the experimental observations, the thyroid is held to be a factor in maintaining the normal periodicity of gastric hunger contractions. The hypothyroid state was brought about in two dogs by thyroidectomy, the parathyroids and their blood supply being spared. Cachexia and death of the animals occurred after seven and eleven months, respectively. In these animals, the hunger contractions were also increased in amplitude and frequency during the stage of cachexia. The increased gastric motor activity, which is ascribed to the trophic skin lesions present, was associated with ravenous appetite, in spite of which, however, the cachexia was progressive. The latter state is held to be the result of faulty resorption and assimilation from the intestine, due to trophic disturbances in the mucosa.

O T SCHULTZ

CORPUS LUTEUM AND AMENORRHEA G A WAGNER, *Zentralbl f Gynak* **52**
10, 1928

The function of the corpus luteum consists in the pregravid preparation of the endometrium and the preservation of the status through the prevention of a hemorrhage in the hyperemic mucosa. The menstrual hemorrhage occurs after the corpus luteum ceases to function. Persistence of a corpus luteum may result in amenorrhea without pregnancy. The impregnated reimplanted ovum acts with increasing intensity also directly on the endometrium toward the prevention of hemorrhage. During the first two months of pregnancy the functional activity of the ovum usually is not able to prevent the onset of a hemorrhage after removal of the corpus luteum. Exceptions to this rule occur occasionally. The death of the nonimpregnated ovum does not cause the degeneration of the corpus luteum. This occurs at a later date than the death of the ovum. The corpus luteum regresses after a predetermined period has elapsed if no new stimulus from an impregnated reimplanted ovum keeps it alive. Wagner describes a case of amenorrhea in which he removed a corpus luteum cyst in a mature stage. Implantations from the luteal cell layer into mice produced a positive Allan-Doisy test in these animals. The endometrium was in the pregravid stage of hyperplasia. Persistence of a follicle or a follicular cyst may be responsible for metrorrhagia. The effect of corpus luteum preparations is due to the typical action of the corpus luteum hormone on the endometrium. In a second case of amenorrhea reported, multiple luteal cysts were found. The patient had all the signs of pregnancy. During the recovery from the operation the diagnosis of a benign adenoma of the anterior lobe of the hypophysis was made. The possibility of relations between this tumor and the luteal cysts on the basis of the observations of Zondek and Aschheim is considered.

W C HUEPER

PARATHYROID TUMOR I SNAPPER, *Nederl Tijdschr v Geneesk* **73** 4758, 1929

In a man, aged 56, who was affected with marked decalcification of the bones, associated with severe pains, particularly in the legs and knees, it was found that the disease had begun as generalized osteitis fibrosa cystica. There was a pseudo-

osteomalacic end-stage resembling that of Recklinghausen's disease. The calcium content of the blood serum was much increased, which was interpreted as an expression of an overactive parathyroid. There was a small tumor in the thyroid. A tumor in one of the parathyroids was suspected and was found at operation. After extirpation of this small tumor, a decided improvement in the patient's condition, amounting practically to a clinical recovery, was noted.

Pathologic Anatomy

PREMATURE INFANTS NORMAN W. CIGIN, *Am J Dis Child* **37** 751, 1929

Certain pathologic lesions produce a constant symptom-complex in the infant. Other pathologic lesions in the same infant apparently do not cause regular symptoms. The former lesions may be referred to as the chief cause of death, because of the fact that they consistently cause the same definite symptom. Infratentorial hemorrhage invariably causes intermittent cyanotic attacks.

Infratentorial hemorrhage occurred in 50 per cent of the cases in which necropsy was performed: otitis media, in 166; atelectasis, in 83; syphilis, in 111; and tuberculosis, in 55.

Pathologic lesions other than the chief lesion usually do not produce any characteristic clinical symptoms. These lesions include cortical hemorrhage, moderate degrees of atelectasis, patent foramen ovale and ductus arteriosus and mild infection. Atelectasis and infratentorial hemorrhage affect chiefly the most immature infants. Both conditions usually cause death within the first three days.

Acquired infections occur in older and heavier infants, usually after the first two weeks. The infants with tuberculosis and syphilis were older and heavier and died at a later age than the infants in the other groups.

The infants admitted when new-born or when 1 or 2 days of age who died shortly thereafter showed definite signs of immaturity of the tissues and organs. The usual cause of death was intracranial hemorrhage or atelectasis.

The infants admitted after the first week were heavier and older. The more immature infants had already died. These older infants were sent to the hospital because they were not doing well, chiefly on account of poor feeding formulas or infection.

AUTHOR'S SUMMARY

LATE DEATH AS A RESULT OF CEREBRAL HEMORRHAGE AT BIRTH. JEROME GLASER, *Am J Dis Child* **37** 807, 1929

The author reports a case of cerebral hemorrhage in which death occurred one month after birth. The hemorrhage evidently happened at the time of birth, the delayed symptoms and resulting death were the results of the organization of the blood clot around the medulla. The hemorrhage was limited to the base of the brain, pons, medulla and cerebellum.

HARRY E. LANDT

CONGENITAL DUODENAL STENOSIS AND ATRESIA. ADOLPH G. DE SANCTIS and JOHN DORSEY CRAIG, *Am J Dis Child* **37** 818, 1929

The condition in the case herein reported was diagnosed during life as pyloric stenosis. Laparotomy and exploration failed to reveal pyloric stenosis or any visible pathologic change which would explain the coexisting symptoms. Intramural duodenal stenosis was found on postmortem examination. Duodenal stenosis or atresia is probably more common than formerly thought. Congenital duodenal stenosis or atresia should be considered in any case of persistent vomiting of an apparently obstructive type during the first weeks of life or in any case presenting an atypical picture of the symptom-complex of pyloric stenosis.

AUTHORS' SUMMARY

DISSEMINATED SARCOMATOSIS (MELANOBLASTOMA?) OF THE CENTRAL NERVOUS SYSTEM AND THE MENINGES GEORGE B. HASSIN and PETER BASSOI, Arch Neurol & Psychiat **21** 1087, 1929

The outstanding complaints in the patient, aged 37, were pains in the legs inability to walk, urinary disturbances and vomiting. The vision in the right eye was poor, the right optic disk was swollen and the right pupil reacted sluggishly to light, the tendon reflexes were absent throughout, the superficial reflexes were retained and on spinal puncture no fluid was obtained. The condition grew progressively worse, the paralysis became complete, the right eye became blind, the right pupil ceased to react to direct light and the sensibility was almost lost in both lower extremities. Yet the pain persisted. The necropsy revealed among other changes nodules in the peritoneum, lungs, pleura, endocardium and pericardium, small intestines, brain, cerebellum, in the stalk of the pituitary body and especially around the cauda equina. Here a soft, grayish-red tumor extended from the twelfth thoracic vertebra to the upper border of the sacrum, it entirely filled the bony canal and infiltrated the dura, the nerves and the filum terminale.

Microscopic studies showed that the tumor cells densely enveloped ringlike, the cauda equina, entirely filling up the subarachnoid space, thus causing the absence of fluid on spinal puncture, the tumor masses were vascular and cellular. Some cells contained melanin pigment which was also present in the adventitial spaces of the blood vessels, the majority of the tumor cells (of the dura, brain, stalk of the pituitary body) contained no pigment and appeared colorless. The spinal cord was not invaded by the tumor and showed no signs of compression or disfiguration. It exhibited areas of rarefaction, especially in the posterior columns of the lumbosacral cord and their degeneration in the upper thoracic and cervical regions. The changes were not unlike those seen in tabes dorsalis. It was not possible to determine the exact nature and place of origin of the tumor. It originated most likely in the cerebellum, from where it was carried along the perivascular spaces to the subarachnoid, cerebral and spinal space. Here it involved the meninges, the spinal roots and the cauda equina. The circulating spinal fluid carried the cells of the tumor along the perineural root spaces into the general circulation and set up lesions elsewhere in the body. The presence of pigment suggested a melanotic tumor. The numerous classifications which were offered for the type of the tumor described are mentioned, and references are made to the extensive literature.

G. B. HASSIN

THROMBO-ANGITIS OBLITERANS (SPERMATIC VESSELS) A. LEF. MCGREGOR and F. W. SIMSON, Brit J Surg **26** 539, 1929

A Russian Jew, aged 28, presented yellowish-brown nodules at the upper and lower ends of the epididymis with slight generalized thickening of the cord and the epididymis. The veins were more involved than the arteries which the authors attribute to the rich venous return of this portion of the body. Microscopically, the picture is rather unique in that the changes vary from the acute to the chronic stages. The vessel coats were infiltrated by acute inflammatory cells, and the lumens were occluded by red clots which contained purulent foci, and in the vessels involved for a longer period of time there were organized masses that contained angioblasts and giant cells. In those in which the process was more advanced, distinct canalization of the intravascular substance was present. The authors do not mention the possibility of the periarteritis nodosa which must be considered in view of the acute inflammatory changes involving the arterial walls and the surrounding tissue, but, as the authors noted, the marked involvement of the veins as compared to the arteries is somewhat against that possibility.

RICHARD A. LIFVENDAHL

CHOKED DISK W. KYRIEIS, Arch f Ophth **121** 560, 1929

Choked disk can occur in certain diseases of the blood, as the result of definite ocular changes as well as following increased intracranial pressure. Of the blood disorders, it occurs most frequently in chlorosis and in polycythemia. When choked disk is present, lumbar puncture shows that the pressure in the cerebrospinal fluid is from 100 to 300 mm (of water) higher than normal. An ophthalmoscopic picture that cannot be distinguished from choked disk accompanying increased intra-ocular pressure can be present when the eyeball is greatly softened from a perforating injury, operation or ulcer, from a severe contusion of the eye or in a shrunken globe. Here the author thinks the mechanical factor exerted by the partial vacuum within the eyeball is important.

CHARLES WEISS

FAT CONTENT OF LYMPH NODES BARBARA JAEGER, Beitr z path Anat u z allg Path **80** 15, 1928

In a morphologic study of the fat content of normal lymph nodes, axillary, inguinal and mesenteric lymph nodes were selected for examination. Fat was found to be present in all the groups studied in the form of fine dustlike particles, granules and larger droplets. It was present between the cells, as well as within the sinus endothelia, the reticuloendothelial cells and the lymphocytes. None was found in the germinal centers. It was present in slightly greater amount in the mesenteric nodes than in the other groups. The nodes of children and of those dead of wasting diseases contained a somewhat greater amount of fat than those of normal persons or of persons dead of acute disease. According to its staining reactions the material present was mixed fat and cholesterol esters.

UNUSUAL HEART ANOMALY O. JAEGER, Beitr z path Anat u z allg Path **80** 29, 1928

The author describes a heart obtained at necropsy from a girl, aged 9 months, and discusses the genesis of the anomaly in the light of the phylogenetic atavism theory propounded by Spitzer in 1923. The interventricular septum was defective. The right auriculoventricular valve was a typical mitral, the valve of the left side being a tricuspid the posterior segment of which was adherent to the posterior portion of the defective septum. The left tricuspid valved ventricle gave rise to the aorta, situated to the left and the pulmonary artery, situated to the right. The ductus arteriosus was patent. In the features noted the heart was an example of the not uncommon type of dextroversion, inversion and transposition, which has formed the strongest support for Spitzer's theory. The unusual feature of the heart described consisted in the presence of chordae tendinae which ran from the posterior segment of the tricuspid valve, which was situated in the left sided ventricle, through the defect in the septum, to be inserted in a strong papillary muscle on the posterior wall of the right sided ventricle. The author believes that this papillary muscle was developed from the anlage of the posterior portion of the interventricular septum, the posterior portion of the existing septum having arisen from new formative tissue which began its development after the original septal anlage had begun to be transformed into papillary muscle. In this feature as well as in the other anomalies present, the author believes the heart to offer strong support for the Spitzer theory.

LYMPHOGRANULOMATOSIS OF THE MAMMARY GLAND H. KUCKENS Beitr z path Anat u z allg Path **80** 135, 1928

In a girl, aged 16 years, swelling of the right breast was noticed several weeks before operation. At this early stage the lesion was thought to be a tuberculous abscess secondary to tuberculosis of a rib. Progressive involvement of the entire breast and induration led to a later diagnosis of a malignant condition. The surgically removed tissue, when submitted to microscopic examination, was found

to consist of characteristic Hodgkin's granuloma with eosinophils, plasma cells and Dorothy Reed-Sternberg giant cells. Most of the glandular tissue had been replaced by the granulation tissue. The latter had diffusely invaded the underlying pectoral muscle and had extended to the left of the midline. No involvement of any lymph node group could be detected on later careful examination, and the author considers the case one of primary localization of lymphogranulomatosis in the mammary gland and the only case of this kind recorded in the literature. Kauffmann describes a case of axillary lymph node lymphogranulomatosis which involved the mammary gland and pectoral muscle by direct extension.

EFFECT OF CHOLESTEROL FEEDING ON THE LIVER AND SUPRARENAL GLANDS OF THE RABBIT. H. RINECK, Beitr z path Anat u z allg Path **80** 145, 1928

Because of discordant results obtained by previous investigators, Remeck made a study of the effects of prolonged cholesterol feeding on the liver and suprarenal glands of rabbits, paying especial attention to normal variations in these organs and to factors other than cholesterol which might influence the lipid content of the organs. The normal content of the suprarenal cortex in anisotropic substance was greater in winter than in summer. The oil in which the cholesterol is administered through its influence on the general nutrition of the animals, impurities in the cholesterol, the character of the food, the conditions under which the animals were kept, all were found to influence the amount of anisotropic material stored. Sesame and linseed oils when used as solvents for the cholesterol were found to have an adverse effect on nutrition, peanut oil, olive oil and mixtures of the two were much more satisfactory. When all the factors which might vitiate the effects of cholesterol were carefully controlled the content of the suprarenal cortex in anisotropic material increased as the blood cholesterol increased. Like the latter it reached a maximum limit beyond which further cholesterol administration had no effect. Anisotropic material made its appearance in the liver at a time considerably after a definite increase could be seen in the suprarenal gland. The quantity never became great, the material was present in both Kupffer cells and liver parenchyma. Cholesterol storage by the liver and suprarenal glands caused no apparent harm to the cells. When other agencies injured the cells, the quantity of cholesterol stored became greater than when such damage was excluded. The suprarenal cortex is held to be a regulatory mechanism in the metabolism of cholesterol, but its action in this respect is a limited one.

FATTY CHANGE OF MYOCARDIUM. H. RINECK, Beitr z path Anat u z allg Path **80** 186, 1928

The literature relating to fatty change of the myocardium is reviewed, with especial reference to the question as to whether such change is ever physiologic. Microscopic study of 130 hearts of persons ranging in age from 1 month to 90 years led the author to conclude that the presence of fat within the muscle fibers of the heart is never an alimentary process; that the presence of fat is due to abnormal metabolism of the muscle fiber and that fat even when present in minimal amounts is pathologic.

PULMONARY SILICOSIS IN JAPAN. T. UCHIYAMA, Beitr z path Anat u z allg Path **80** 218, 1928

Silicosis of the lung is a rare condition in Japan, probably because not many persons are engaged in stone cutting. The author reviews the literature of the subject, especially that dealing with the relation of silicosis and tuberculosis to each other, and reports three cases studied by him. These three cases occurred in a total of 1,500 necropsies in a ten year period. In one of the three cases the process was marked, in one it was slight and in all it was associated with

tuberculosis. The latter was more fibrotic in the lungs with the most marked grade of silicosis. The three patients were of the thymicolymphatic type, in which connective tissue proliferation appears to be greater, according to the author, than in other constitutional types. The tuberculous involvement of the lungs appeared to have been held in restraint by the silicotic process. In the case with the most marked pulmonary silicosis small tubercle-like nodules were present in the liver and spleen. These were not tubercles, but silicotic nodules formed about spicules of the foreign material indicating that the inhaled material may be transported by the blood stream.

ANNULAR PANCREAS. H. SMETANA. Beitr. z. path. Anat. u. z. allg. Path. **80** 239, 1928.

The author reports three cases of annular pancreas: one in a child, 1 month old, one in a man, aged 70 and one in a man aged 74. The last patient was admitted to the hospital with symptoms of acute intestinal obstruction which were found to be due to constriction of the duodenum by the encircling ring-shaped head of the pancreas. The 70 year old man was admitted for empyema. The annular pancreas was observed at necropsy. The head of the organ encircled the duodenum constricting the latter to such a degree that the lumen would barely admit the tip of the finger. The duodenum above the constriction was dilated and the mucosa was ulcerated. Clinical symptoms of intestinal obstruction were probably overlooked because of the empyema. In the child the annular pancreas had not caused narrowing of the duodenum. Careful dissection of the ducts showed in each case that the duct of the duodenal portion of the pancreas was the main duct of Wirsung and emptied at the papilla of Vater. The author reviews the previously reported twenty-four cases of annular pancreas and discusses the theories of origin of the anomaly. These included abnormal development of the ventral anlage of the pancreas, premature union of the ventral and dorsal anlage due to delayed rotation of the stomach and duodenum and abnormal shortness of the main pancreatic duct. The anomaly need not cause narrowing of the lumen of the duodenum, as was evident in the child 1 month old. Narrowing may develop later as the result of the failure of the part of the duodenum surrounded by the pancreas to take part in the normal peristalsis of the duodenum. Diabetes has been noted in a few cases of annular pancreas and the pancreatic anomaly has been associated with other maldevelopments in a number of the reported cases.

ACQUIRED EPITHELIAL HETEROTOPIA OF THE GASTRO-INTESTINAL TRACT. H. HAMPERL, Beitr. z. path. Anat. u. z. allg. Path. **80** 307, 1928.

Under epithelial heterotopia of the gastro-intestinal tract Hamperl discusses the occurrence of islands of epithelium of a kind not normal for the situation in which it is found. The forms recognized are (1) squamous cell heterotopia, (2) ciliated cell heterotopia, (3) intestinal epithelial heterotopia of the gastric mucosa and (4) mucous cell or pseudopyloric heterotopia of the gastric mucosa. Two forms of squamous epithelial heterotopia are seen: that in which defects in cylinder cell epithelium are replaced by squamous epithelium by direct growth of the latter at a normal junction of squamous and cylinder epithelium, as at the esophagogastric junction and at the anorectal junction, and that in which islandic defects in a cylinder cell epithelium are replaced by squamous epithelium which has no connection with pre-existing epithelium of the same type. The presence of ciliated epithelium in carcinomas of the stomach has been described by several observers, and the author presents an example of the presence of a local area of such epithelium in the noncarcinomatous gastric mucosa. He doubts, however, that such epithelium is true ciliated epithelium, but thinks that the ciliated appearance of the cells is not due to the presence of true cilia but to the loss of the cuticular zone of cylindric epithelium. The most frequent heterotopias are those in which islands of intestinal glands occur in the gastric mucosa or glands

of pyloric type are found in the mucosa of the fundus of the stomach. Such changes are usually associated with chronic gastritis, but they are probably the result rather than the cause of the gastritis. True metaplasia of one type of epithelium into another is not the explanation of the acquired heterotopias seen in the gastro-intestinal tract. They are due, rather, to local loss of normal epithelium, which is replaced by indifferent regenerating epithelium. The latter has the potentiality of differentiating into epithelium normal for the situation or into epithelium which is heterotopic. Which course the differentiation will take depends on the physicochemical factors to which the regenerating epithelium is subjected.

LESIONS OF THE AORTA IN RHEUMATIC FEVER H. CHIARI, Beitr z path Anat u z allg Path **80** 336, 1928

The author discusses briefly the literature relating to the occurrence of granulomatous lesions, similar to Aschoff bodies, in tissues other than the myocardium. He states that lesions of the aorta and larger arterics have been described by few writers. He is apparently unfamiliar with the important recent American literature on this subject. In six of seven cases of rheumatic fever, the patients having died during acute exacerbations of the disease, he found involvement of the aorta and its larger branches. The lesions were situated in the adventitia and were of three types. Small, nodular, infiltrative lesions about the vasa vasorum consisted of lymphocytes, plasma cells, mast cells and large polygonal cells called fibroblast-like, but differing from fibroblasts in the chromatin distribution within the nucleus and in the basophilia of the cytoplasm. In somewhat larger, flatter lesions in the inner zone of the adventitia, a perivascular arrangement could not be seen. In such areas plasma cells and lymphocytes were less numerous than in the smaller lesions, but the large cells were more numerous and occurred as uninnucleate or multinucleate giant cells. Still larger and more widespread lesions of the same composition were also seen in the inner zone of the adventitia. The larger lesions often contained fibrin at their centers, but no polymorphonuclear leukocytes. The author thinks that exudation, leading to fibrin deposition, is a later process than cellular infiltration and proliferation. In one case the lesions were older and had become partly hyalinized. In the case in which no aortic lesions were seen the myocardium was free from Aschoff bodies, and the author considers it possible that this may not have been a rheumatic infection. In his discussion of the nature of the vascular lesions described, Chiari mentions a similarity to periarteritis nodosa and to syphilitic mesaortitis. The former attacks the small arteries rather than the aorta, and syphilis involves the ascending aorta rather than the descending or abdominal portion, in which the rheumatic lesions had their situation. The media showed no changes, small areas of slight intimal proliferation were seen in the aorta. The author concludes that the vascular involvement described by him is characteristic of rheumatic fever and is probably due to hematogenous localization of the specific virus.

GASTRO-INTESTINAL LYMPHOGRANULOMATOSIS AND ICTERUS DUE TO LYMPHOGRANULOMATOSIS C. CORONINI, Beitr z path Anat u z allg Path **80** 405, 1928

The author reports in detail a study of five cases of Hodgkin's lymphogranulomatosis with chief involvement of the gastro-intestinal tract, and five cases of generalized lymphogranulomatosis associated with jaundice. Gastro-intestinal lymphogranulomatosis is classified as that involving the gastro-intestinal tract alone, that involving the tract chiefly and that which is part of a generalized process. In each group are placed cases of her own and from the literature in which the stomach alone was involved, cases with intestinal involvement alone and those in which lesions occurred in both the stomach and the intestine. Icterus in lymphogranulomatosis is obstructive and may be due to compression or obliteration of the common duct alone, to changes in both extrahepatic and intrahepatic ducts.

or to changes limited to the intrahepatic ducts. The gastro-intestinal lesions consist of nodules which arise in the submucosa and form flattened masses which protrude in the lumen and which become superficially ulcerated, of smaller nodules scattered throughout the wall, and of broad areas of granulomatous tissue which invades the wall of the stomach or intestine widely and diffusely. Especial attention is given to a discussion of changes in the blood and the lymph vessels. The author describes proliferation of the endothelium of lymphatic channels and sinuses and of capillaries as the first stage in the formation of the lymphogranulomatous nodules and ascribes to such proliferated endothelium the chief role in the formation of the granulomatous tissue. In the arteries proliferation of adventitial cells may take part in the process. In both arteries and veins invasion from without may occur, or endothelial and subendothelial proliferation may lead to the formation of obliterating nodules. The latter are rarely penetrated by newly formed capillaries. Obstruction of the extrahepatic bile ducts may be due to pressure of enlarged lymph nodes or to invasion of the wall by granulomatous tissue. Within the liver the interlobular ducts may become compressed by the involvement of the interlobular stroma.

CONCRECTIONS OF SEMINAL TUBULES. I. OBER, Beitr. z. path. Anat. u. z. allg. Path. **80** 479, 1928

In the histologic examination of over 300 pairs of human testes, the author saw calculi within the seminterous tubules in six cases. When present the calculi were multiple, they had a maximum size of 200 microns, they gave the micro-chemical reactions for calcium and iron, and they were not dissolved by acids strong enough to cause swelling of the surrounding tissue. They were usually situated within the lumen of the tubule but in a few instances had made their way into the interstitial tissue. The author ascribes their origin to desquamated epithelial cells, although coagulation of tubule contents may have played a part in their formation. They were laminated but did not give the reaction for amyloid. Although calculi are frequently seen in the epididymis, seminal vesicles and prostate, the author claims that they have not previously been reported within the testis itself.

ACUTE PEPTIC DUODENITIS. F. BUCHNER and F. KNOIZKI, Beitr. z. path. Anat. u. z. allg. Path. **80** 496, 1928

The authors made a histologic study of three surgically resected specimens of duodenum, especially with the view of determining whether minute hemorrhages or infarctions play a part in the formation of the early peptic lesions seen in the duodenal mucosa. The lesions present varied from fresh superficial erosions to acute ulcers extending through the mucosa. No relationship to hemorrhage or infarction could be detected, and the authors ascribe the lesions to the direct action of the gastric juice. They believe that a previously normal mucosa may be injured by a gastric juice which is abnormal qualitatively or quantitatively or because of a failure of proper neutralization by pyloric or duodenal secretion. They consider the duodenal lesions seen by them similar to those described many years ago by Nauwerck as peptic gastritis.

AMITOSIS, PHYSIOLOGIC REGENERATION AND REJUVENATION. M. STAMMLER, Beitr. z. path. Anat. u. z. allg. Path. **80** 512, 1928

The discovery of karyokinesis relegated amitosis to the background as a process of importance in the life activities of the cell. In 1849, Bizzozero divided the tissues of the body into those in which mitosis occurs under normal conditions, the process leading to replacement of exhausted elements, that is to physiologic regeneration, and into those in which mitosis did not normally occur and which therefore were not capable of physiologic regeneration. The first group contained most of the secreting glands, the second group the rest of the tissues. Pathologists in general have accepted the idea of Bizzozero and divide tissues into those in

which cellular replacement or regeneration occurs as a physiologic process, those in which regeneration does not occur under normal conditions but is possible under pathologic stimulation, and those in which even pathologic stimulation cannot cause regeneration, the ganglion cells of the central nervous system and the cardiac muscle being placed in the last group. Staemmler made a study of tissues in which physiologic replacement of cells has been held not to occur. The tissues studied included cardiac muscle, voluntary muscle, liver parenchyma, and renal tubular epithelium. The voluntary muscle studied was from the tongue, diaphragm, and psoas. In all the tissues investigated he found cells with two nuclei, and even with four nuclei, to be numerous. He describes and depicts the binucleate or multinucleate condition as resulting from amitotic nuclear division. The binucleate condition was seen more frequently in adults than in children. In some of the tissues, especially cardiac muscle, the amitotic formation of new nuclei apparently has a periodic rhythm. How the number of nuclei thus formed is again reduced could not be definitely determined; apparently all the nuclei did not take part in the formation of new cells, because division of the cell body of binucleate cells was only infrequently seen. In cardiac muscle Staemmler considers cellular division to be unessential for regeneration because the tissue is a syncytium. In voluntary muscle nuclear division may be a factor in the longitudinal growth of the muscle fiber. He looks on amitosis as a process which leads to rejuvenation of cells which delays the physiologic senescence and death of the cells, and which leads to the physiologic replacement or regeneration of cells exhausted by the performance of their normal functions. Each subdivision of his article opens with a valuable and concise review of the literature, biologic as well as pathologic, relating to the subject matter under discussion.

CHOLESTEROL FEEDING OF OMNIVORA. D. YLASEN, Beitr. z. path. Anat. u. z. allg. Path. **80** 570, 1928.

In most of the experimental work the aim of which has been the study of the effects of prolonged cholesterol feeding the rabbit, an herbivore, has been the animal of choice. The author questioned whether the results obtained, especially those relating to cholesterol arteriosclerosis in the rabbit, could be transferred to man, an omnivore, without reservation. He therefore studied the effects of prolonged cholesterol feeding on several species of omnivorous animals, namely, rats, mice, cats and one fox. The results in general were identical with those obtained by most previous observers in the case of the rabbit. The intima of the aorta is the site of predilection for deposition of anisotropic cholesterol esters. The latter are deposited also in the liver and in the cells of the reticulo-endothelial system, as in the rabbit. The author concludes that it is proper to use the results obtained in cholesterol experimentation on the rabbit in the elucidation of human pathology.

LOCAL EFFECTS OF VENOMOUS SNAKE BITE. W. BERBLINGER, Beitr. z. path. Anat. u. z. allg. Path. **80** 595, 1928.

Bites by venomous snakes being infrequent in Germany, Berblinger reports the results of the histologic study of the local skin and subcutaneous reaction about a bite due to the viper, *Vipera berus*. The venom causes necrosis of the tissues with which it comes in contact, especially the capillaries. Hemorrhage and edema result. The predominant exudate cell is the polymorphonuclear leukocyte. The process set up by the bite is an exudative inflammatory reaction, in which the exudative phenomena are already well marked within an hour.

CONGENITAL DIAPHRAGMATIC DEFECT WITH UPWARD DYSTOPIA OF KIDNEY. H. O. KLEINE, Beitr. z. path. Anat. u. z. allg. Path. **80** 609, 1928.

The author presents an example of diaphragmatic defect in a female infant who lived twenty-four hours. The gastro-intestinal tract from stomach to sigmoid

was situated in the left pleural cavity as was also the spleen. The defect in the diaphragm was limited to the left side. The left suprarenal and the upper pole of the left kidney extended through the defect into the pleural cavity. Pleura and peritoneum were united at the margins of the defect. The misplaced abdominal organs were not covered by parietal peritoneum, the condition therefore not being one of true hernia. The right lung was compressed and atelectatic, the heart was pushed to the right and there was scoliosis of the thoracic vertebral column to the right. Foramen ovale and ductus arteriosus were patent. The total mobile mesocolon had persisted, resulting in a mesenterium commune which permitted the entire intestinal tract to enter the thoracic cavity. The dystopic kidney, however, was firmly attached to its underlying retroperitoneal tissue. The renal kidney in its normal ascent reaches the diaphragm at or just before the time of closure of the pleuroperitoneal foramen. Kleime believes that a more rapid ascent of the kidney than normal prevented closure of the foramen and was the causative factor in the diaphragmatic defect. Ten previously reported cases of diaphragmatic defect with renal dystopia together with his case constitute a special group in which the renal dystopia was the cause of the defect. Persistence of the mesocolon may be the cause of the abnormal ascent of the kidney.

TISSUE CHANGES DUE TO REDUCED OXYGEN TENSION. A. ROSEN. Beitr. z. path. Anat. u. z. allg. Path. 80: 622, 1928.

In a previous communication Rosen had described marked fatty change of the liver and myocardium as the result of a reduced oxygen supply. Such changes had been noted in guinea-pigs but not in mice. David had raised the objection that the results obtained were due to the reduced atmospheric pressure under which the animals were kept and not to reduced oxygen supply. In the present work the atmospheric pressure was maintained at normal but the oxygen tension was reduced. The animals used were rabbits, rats and chickens. Rabbits were found to react like the guinea-pigs of the earlier experiments in the development of marked fatty change of the liver. Rats were unaffected, being in this respect like the mice of the previous work. Chickens also showed no changes. In the liver of rabbits and guinea-pigs the fat was present in the central zone, glycogen being present in the peripheral zone of the lobules. Many of the cells of the central zone became necrotic. Splenectomy did not alter the results. High transection of the spinal cord caused no fatty change in rabbits under normal oxygen relations but the characteristic changes occurred when such animals were subjected to lowered oxygen tension.

MULTINUCLEATED CELLS IN THE SEMINAL TUBULES. T. OLIVE. Beitr. z. path. Anat. u. z. allg. Path. 80: 645, 1928.

In a study of a large series of human testes Olive occasionally saw multinucleated cells in the seminiferous tubules. They may be derived from the Sertoli cells or from the spermatogenic cells, rarely by nuclear division without cell division but more frequently by fusion of cells. The process is the result of degenerative changes in the cells.

MULTINUCLEATED GIANT CELLS IN THE SEMINAL TUBULES. A. F. KRAUS. Beitr. z. path. Anat. u. z. allg. Path. 80: 658, 1928.

The multinucleated giant cells sometimes seen in the seminiferous tubules of the human testis are formed from the seminal cellular elements by fusion of the cells. According to the characteristics of the nuclei, Kraus recognizes three types of giant cells: those due to fusion of spermatids, of spermatogonia and of spermatocytes. They are formed as the result of injury to the seminal epithelium, the spermatid giant cells being formed after the slightest grades of abnormal conditions. The giant cells are cast off into the lumen of the tubule and disintegrate.

LEIOMYOMA OF ENDOCARDIUM WITH OCCLUSION OF PULMONARY ARTERY
H ESCHBACH, Beitr z path Anat u z allg Path **80** 672, 1928

A man, aged 58, had first complained of symptoms referable to the heart a year previous to his final admission to the hospital. At that time a diagnosis of aortic stenosis was made. When admitted he complained of loss of appetite, strength and weight, and of pain in the epigastrium, symptoms which led to a probable clinical diagnosis of carcinoma of the stomach. He was cyanotic, there was slight clubbing of the fingers, a systolic murmur could be heard over the entire cardiac area and the heart was enlarged on percussion. There was no evidence of tuberculosis. Ten days before death, he suddenly collapsed and complained of pain in the chest. The pulse was rapid and small. A probable diagnosis of infarction of the lung was made. At necropsy, the enlargement of the heart was found to be due chiefly to increase in the size of the right ventricle. The diameter of the root of the pulmonic artery was greater than that of the root of the aorta. Arising in the conus of the pulmonic artery about 2 cm below the pulmonic valve was a firm, pale, tumor mass, which had grown upward, involving the segments of the valve, and had extended into the pulmonic artery. The growth extended in the branches of the left pulmonic artery into the lung, which was collapsed. Microscopically, the tumor was composed of dense, hyaline areas, and of other more cellular parts which contained smooth muscle, as determined by the van Gieson stain. The tumor did not appear invasive, its growth occurring in the lumen of the conus and of the pulmonic artery. The origin of the tumor was ascribed to the smooth muscle normally present just beneath the endocardium immediately below the pulmonic valve.

INTRAMESENTERIC MECKEL'S DIVERTICULUM SIMULATING REDUPLICATION OF THE ILEUM L KUGELMEIER, Beitr z path Anat u z allg Path **80** 682, 1928

A girl, aged 5 months, who died of hemorrhage from a congenital ciliated cyst of the lung, had what appeared to be a longitudinal reduplication of the ileum. Beginning at a point 12 meters above the ileocecal valve was a tubular structure 50 cm long. This was situated within the mesentery, its two-layered smooth muscle wall being in apposition with the muscle wall of the ileum. The structure ended blindly above, the blind end being somewhat dilated. No connection with the umbilicus could be detected. The microscopic structure was like that of the ileum. The author considers the structure described an unusually long Meckel's diverticulum, and believes that the small number of reported cases of longitudinal reduplication of the ileum are likewise examples of intramesenteric Meckel's diverticulum. (The abstracter has seen an exactly similar case of apparent reduplication of the ileum, this was held to be an unusually long Meckel's diverticulum.)

SPONTANEOUS BILATERAL PNEUMOTHORAX IN A CASE OF POLYCYSTIC LUNG
A SCHMINCKE, Beitr z path Anat u z allg Path **80** 692, 1928

A woman, aged 24, developed bilateral pleural effusion about a year before her admission to the hospital. The fluid was clear and contained no cells or tubercle bacilli. The difficulty in respiration with which she suffered was relieved by withdrawal of the fluid, but returned and was her chief complaint on admission. At this time she was found to have bilateral pneumohydrothorax. No evidence of tuberculosis could be found. The respiratory difficulty was again relieved by withdrawal of the fluid, but recurred from time to time as the fluid reaccumulated. She died after continuation of such symptoms for three fourths of a year. At necropsy, the lungs were compressed and each pleural cavity contained air and free, clear fluid. There were no adhesions and no tuberculous lesions. Beneath the pleura of each lung were numerous air-filled blebs some of which had perforated through the covering pleura, thus giving rise to the pneumothorax.

The dilated air spaces were limited to the peripheral portions of the lungs and were in communication with the bronchial system. They were the dilated portions of the incompletely developed terminal bronchi. Accepting Bender's description of the development of the lung, Schmincke concludes that terminal embryonic bronchi in the peripheral portions of the lung, which are the last portions to complete their embryonic development, did not go on to the formation of an alveoli. The process is considered one of inhibition or Hemmung of fetal development, and Schmincke calls attention to the similarity of the condition described by him, considered the first reported case of its kind, to fetal bronchiectasis and congenital cystic lung, for which embryonic maldevelopment of the kind described offers the best explanation. Cystic dilatation of the undeveloped bronchi, in the walls of which there is little elastic tissue, follows. A case of spontaneous bilateral pneumothorax, identical with that reported by Schmincke, has been briefly described in Abt's "Pediatrics," vol. 4, chapter 65 p. 33.

MULTIPLE CORTICAL NECROSIS OF THE KIDNEY IN PURPURAL SEPSIS. H. GAKFIS-DOLNITZSIUM, Beitr. z. path. Anat. u. z. allg. Path. **80** 697, 1928

In a woman, aged 36, who died of staphylococcal sepsis following her eighth delivery, the surface of each kidney was studded with numerous sharply defined, small, grayish, opaque areas of necrosis. These were limited to the cortex, through which they extended in the form of narrow streaks and wedges. Microscopically, the tissue elements within the areas were in a state of coagulation necrosis and there was only slight leukocytic infiltration at the margins. The arteriae rectae and the vasa efferentia were occluded by hyaline thrombi, about which the tissue of the vessel wall was necrotic, but without leukocytic reaction. Bacteria could not be seen in the lesions. The author interprets the process as a deficient cellular protective mechanism in the presence of increased humoral bacteriolysis, the liberated endotoxins leading to necrosis and thrombosis of the vessels.

O. T. SCHULTZ

A SYMPOSIUM ON CONGENITAL SYPHILIS. Verhandl. d. deutsch. path. Gesellsch. **23** 144, 1928

G. Herzheimer-Wiesbaden declared that from 2 to 4 per cent of infants in large German cities have congenital syphilis. From 1910 to 1920 the frequency was constant; in 1922, there was an increase and during 1926 and 1927 there was a slight decrease. P. Schneider-Darmstadt discussed syphilitic osteochondritis as

Comparison of Incidence of Spirochetes and Lesions

	Spirochetes			Lesions		
	Stillborn Per Cent	Dying Soon After Birth, Per Cent	Young Infants Per Cent	Stillborn Per Cent	Dying Soon After Birth, Per Cent	Young Infants Per Cent
Liver	100	84	30	20	38	46
Pancreas	84	85	20	25	91	12
Lung	95	91	25	18	50	10
Spleen	96	81	35	15	38	33
Heart	85	55	29	0	8	4
Kidney	90	54	38			

seen from the fifth month of fetal life to four months after birth. Periostitis was found to accompany osteochondritis constantly, at least in the region of the epiphysis. A comparison was made between the incidence of spirochetes demonstrated in them and pathologic changes in various organs.

L. Pick-Berlin presented a case of late congenital syphilitic osteochondritis in a girl, aged 11 years. The long bones had undergone a marked sclerotic reaction following caseogummatous lesions and a certain degree of sclerosis was

also manifest in the ribs, phalanges and vertebrae. Wurm-Tubingen reported congenital syphilitic pulmonary lesions in a young woman. Chronic interstitial pneumonia and caseogummatous alterations were prominent but confined to the right lower lobe. The circumscribed character of the lesions led him to doubt their congenital nature. Danisch-Jena described changes in the sympathetic ganglions. The most constant of these were interstitial inflammation, retarded development of ganglion cells and the presence of spirochetes. He thinks that these changes may subsequently lead to trophic disturbances in the gastro-intestinal tract where the celiac ganglions are involved.

GEORGE RUKSTINAT

THE ORIGIN OF THE HYPOPHYSAL-SUBHYPHYSAL SYNDROME. B. N. MOGILNITSKY, *Virchows Arch f path Anat* 269 1, 1928

In obesity, unrelated to increased nutrition changes are frequently found in the neurohypophysis and the parts of the midbrain closely associated with it. The relation of the changes in the sex organs to obesity in Frohlich's symptom-complex is incidental. There are essential forms of Frohlich's syndrome without injury to the midbrain. Investigation of the metabolic changes should be directed to the stria system and higher centers. In investigating pathologic changes associated with this or that symptom-complex, attention should not be confined to any one particular part of the neuroglandular apparatus. There is a possibility that one part is injured primarily and the other parts are secondarily brought into relationship. On both experimental and morphologic grounds, the possibility is offered that the syndrome of diabetes insipidus is not related to injury of the hypophysis. In acromegaly, the subhypophyseal region and the remaining parts of the cerebrum are unchanged.

GYNECOMASTIA. F. A. BITNA-SCHWACHTO, *Virchows Arch f path Anat* 269 45, 1928

The literature is reviewed, and cases are cited. Gynecomastia occurs following disturbances in the function of the testes and other sex organs such as the prostate, seminal vesicles and spermatic cord. The exact relationships, however, must be determined by experimental means.

THE CHANGES IN THE HYPOPHYSIS FROM VITAMIN B DEFICIENCY. S. A. SATKORNYTZKAJA and W. S. SIMONITSKY, *Virchows Arch f path Anat* 269 54, 1928

In the hypophysis of pigeons, droplets of albuminous material appeared in the protoplasm of the basophilic cells most marked on the twenty-fifth day of disease. After twenty-five days, the vacuolization usually regresses and transitions from the vacuolated to the normal cell types appear in the glands. At the same time vacuoles appear in the eosinophilic cells, but these vacuoles could not be stained with any of many methods tried. The intralobular colloid becomes less in amount and may disappear almost completely, toward the end of the condition it reaccumulates but never to the extent present in the normal gland. The appearance of vacuoles in the cells indicates that there is an increased function related to the carbohydrate metabolism in this disease. The changes are more marked in the male than in the female pigeons and are greater in spring and summer than in winter. In rats the basophils of the hypophysis seem to be increased and the eosinophils diminished. Qualitative changes in the cells are much less in degree since the symptoms of vitamin B deficiency in rats take a long time in appearing, whatever changes there are in the hypophysis of rats are related to the carbohydrate metabolism. The necrobiotic changes in the cells of both pigeons and rats are not characteristic and are probably due to changes in the nutrition.

THE SEDIMENTATION RATE OF THE RED CELLS FROM DIFFERENT PARTS OF THE VASCULAR SYSTEM RAPHAEL GAWRILOW, *Virchows Arch f path Anat* **269** 340, 1928

Determination of the sedimentation rate in blood from various vessels of the body showed that the rate of blood from the veins is longer in internal than in peripheral blood. In the general diminished sedimentation rate this is particularly true. The sedimentation rate of peripheral blood is no index of that of internal blood. The rate depends on the plasma in which the cells are put. The addition of various substances such as sodium chloride and acacia usually led to diminished sedimentation rate. It is concluded that this rate is dependent on the physico-chemical characteristics of the blood plasma.

ACQUIRED SYPHILIS OF THE STOMACH FRANZ WINDHOZL *Virchows Arch f path Anat* **269** 384, 1928

The autopsy material in the Rudolph Hospital of Vienna showed no more gross anatomic gastric changes among syphilitic patients than others. A true syphilitic gastric disease occurred only twice in 386 autopsies of syphilitic patients, in both cases this occurred in the early stages of the disease. Those described as true syphilitic changes are (a) a healed localized syphilitic disease of the stomach wall at the pylorus (b) a diffuse contracted stomach, and (c) a circumscribed syphilitic sclerosis. A diffuse shrinkage of the stomach may occur not only from carcinoma but also from inflammation such as syphilis. The literature is well reviewed.

ATROPHY OF THE TESTES IN PULMONARY TUBERCULOSIS A SYLLA, *Virchows Arch f path Anat* **269** 480, 1928

Examination of twenty-six persons who died from tuberculosis between the ages of 16 and 49 showed atrophic changes of the tubules in twenty-three cases.

TRIORCHISM HENDZEL SCHIEIMER, *Virchows Arch f path Anat* **269** 496 1928

Seventeen cases of this condition were found in the literature to which one new case is added. An embryologic explanation is given.

THE HISTOLOGY OF MYELOID LEUKEMIA AFTER ROENTGEN TREATMENT FRANZ FREUND, *Virchows Arch f path Anat* **269** 501, 1928

It is confirmed that leukemic cells may come from transformation of cells of the loose connective tissue, of vessel walls and of fat cells. Under the influence of the roentgen rays, leukemic cells may change back again into connective tissue cells however, not into normal connective tissue cells but into the kind described in the scar following roentgen treatment. An exhaustive review of the literature is presented.

PERIARTERITIS NODOSA IN ANIMALS K. NIEBERLE, *Virchows Arch f path Anat* **269** 587, 1928

Ten cases have been reported in animals, one in a deer, five in swine, three in calves and one in a dog. The case reported occurred in a calf. The changes were identical with those in the disease in human beings.

NEUROMA-LIKE FORMATION IN A SHRUNKEN GALLBLADDER H. HAMPERL, *Virchows Arch f path Anat* **269** 791 1928

A case is described in which an extraordinary increase in the number of nerve fibers was found in a gallbladder shrunken from years of cholecystitis and cholelithiasis. The picture resembled that of a similar condition described in the shrunken vermiform appendix and in the base of peptic ulcer.

Pathologic Chemistry and Physics

STUDIES IN THE METABOLISM OF ALUMINIUM F P UNDERHILL, F I PETERMAN S L STEFL, E G GROSS, A C KRAUSE and A SPERANDEO, *Am J Physiol* 90 1, 1929

In a series of eight papers on the metabolism of aluminum, there are contained a description of the method used, which permits the quantitative estimation of small amounts of aluminum in biologic material, and a series of results of the several investigations conducted by means of this method. Much of the work was done on dogs. In them it was found that the blood even of fasting dogs contains perceptible amounts, which are increased after feeding diets without added aluminum. With aluminum added, this is promptly absorbed in small amounts after a single feeding, and this absorption continues for variable periods when the aluminum rich diet is continued but eventually the absorption decreases, and with this there is a concomitant diminution in aluminum storage and excretion. The absorbed aluminum is present in the blood, and is stored especially in the liver, brain, kidney, spleen and thyroid. The bile constitutes the principal route of elimination, but after the intravenous injection of aluminum salts, it appears promptly in the urine and lymph as well. The increase in these fluids, however, is not sufficient to explain the total decrease in the blood, and there appears to be tissue storage. With diets rich in aluminum, it is absorbed by the lymph, and is excreted at all levels of the gastro-intestinal tract. The intestinal excretion of aluminum and of phosphorus are quite independent of each other. The aluminum content of tissues in the dog appeared to have a definite relationship to age, as it was present only in minute quantities, if at all, in the embryo, there were detectable amounts in the lungs of 5 day puppies, greater amounts in older animals and considerable quantities in the lungs of old dogs. As regards aluminum in man it may or may not occur in the blood. If present, the amount is small, the maximum found being 0.21 mg per hundred cubic centimeters. The aluminum content of individual specimens varies from time to time within narrow limits. After a diet rich in aluminum there may be a definite increase but this at times is lacking. On diets poor in aluminum, there is never an increase while a decrease in these circumstances is the rule. Aluminum is occasionally found in human urine in small amounts, and these tend to increase after the ingestion of aluminum-rich foods. But even with these it does not exceed 0.5 mg in twenty-four hours. As regards the content of aluminum in human tissues, amounts found in the liver ranged from 0.17 to 1.17 mg per hundred grams, in the kidney, from 0.13 to 0.87 mg. There appeared to be a geographical relationship here, presumably to be ascribed to environmental circumstances (food or water). There appeared to be increased storage with advancing age, the highest content in the liver was found, in one case, to be associated with fatty change in this organ. The report includes the results of analyses of a number of foods. No relationship could be established between the botanical grouping of vegetable foods and their aluminum content, the amounts found were sufficient to be significant. As regards the lethal effects of aluminum, a single lethal dose for rats consisted of from 7 to 8 Gm of aluminum chloride per kilogram. Comparable lethal doses were found for the guinea-pig and rabbit. Symptoms of intoxication came on gradually—loss of appetite, followed by lethargy and depression. Autopsy observations consisted of general visceral congestion degenerative changes of the liver, in rabbits accompanied by what appeared to be peripheral lobular necrosis, gastric distention, with swelling of the mucosa and minute areas of hemorrhage, and the occasional presence of shallow intestinal ulcers.

H E EGGERS

PLASMA PHOSPHATASE IN OSTEITIS DEFORMANS AND IN OTHER DISEASES OF BONE H D KAY, *Brit J Exper Path* 10 253, 1929

Lesions of the bone involving a large portion of the skeleton are accompanied by a rise in the amount of phosphatase in the plasma. In osteitis deformans and

osteitis fibrosa, this increase may be large, from four to twenty or more times the normal

AUTHOR'S SUMMARY

THE INDIRECT REACTION FOR BILIRUBIN IN OBSTRUCTIVE JAUNDICE L. HOLLOS, *Klin Wchnschr* 8 1455, 1929

A discussion of the interpretation of the direct and indirect van den Bergh reactions of the blood serum precedes a report of a patient with obstructive jaundice whose serums gave only the indirect test for bilirubin. These qualitative tests for bilirubin, therefore, are not differential as regards the origin of the jaundice.

EDWIN F. HIRSCH

DISTURBANCES OF FAT RESORPTION IN CIRRHOSIS OF THE LIVER AND OTHER DISEASES H. WENDT, *Klin Wchnschr* 8 1566, 1929

The observation of Burger and Habs that in patients with cirrhosis of the liver four hours after peroral administration of 100 Gm. of olive oil and 5 Gm. of cholesterol there is no lipemia, which in health always occurs is confirmed. Similar disturbances of fat resorption were noted with carcinoma, pericarditis, peritoneal tuberculosis and amyloidosis. Stasis in the portal system is the cause of this disturbance of fat absorption.

AUTHOR'S SUMMARY (in part)

THE K⁺ CONTENT OF PUS AND EXUDATES AND ITS RELATION TO INFLAMMATORY PAIN C. HABLER, *Klin Wchnschr* 8 1569, 1929

The potassium content of pus and exudates increases with the inflammation. Serous exudates with a reaction corresponding to that of the blood serum have a potassium content not greater than that of normal serum. Serofibrinous and seropurulent exudates have as much as one and a half times the normal potassium content. Purulent exudates have as much as from 513 to 205 mg. per cent potassium, and in all of these exudates the potassium content parallels the severity of the inflammation and the degree of acidity. The increase in potassium is ascribed to the extensive destruction of the cells, from which potassium passes into the exudate. Further in the origin of the pain with inflammation potassium is an essential component. With serofibrinous and seropurulent exudates the reaction and osmotic tension of which are in the range that does not provoke pain, potassium is the only cause of inflammatory pain. With acute purulent exudates is the added factor of the high acidity, and this component is coupled with the increase in potassium in provoking pain.

AUTHOR'S SUMMARY

THE EFFECT OF HORMONES IN THE SUGAR DISTRIBUTION AND CELL PERMEABILITY OF ANIMALS R. SIEGEL, *Klin Wchnschr* 9 1655, 1929

Under physiologic conditions insulin furthers the localization of sugars and the glycogen fixation in the liver. In the muscle tissues it increases the penetrability of sugar and increases its synthesis to glycogen with a coincident oxidation of a small fraction. Epinephrine in smallest concentrations under physiologic conditions acts in the liver in the same way as insulin, namely, glycogen fixing. In the periphery of the body it is its antagonist so far as it hinders the transfer of sugar from the blood into the muscle. With glycogen depletion of the liver, epinephrine stimulates the new formation of liver glycogen by increasing the formation of lactic acid from muscle glycogen. Epinephrine has almost no effect on the oxidative destruction of carbohydrates. Only with abnormally high concentrations (shock, experiment) does epinephrine act in the opposite way, that is, breaking down glycogen into sugar through stimulating the sympathetic endings in the liver. Thyroxin in the liver is the real antagonist of insulin and epinephrine, while in the periphery of the body thyroxin has no effects.

AUTHOR'S SUMMARY

THE TRANSPORTATION OF CALCIUM FROM MOTHER TO CHILD AND CALCIFICATIONS IN THE PLACENTA A. SCHÖNIG, *Ztschr f Geburtsh u Gynäk* **94** 451, 1928

Fresh placental tissue was left for twenty-four hours in a saturated solution of ammonium oxalate, to which a few drops of toluene were added, and put into an icebox. The tissue was then transferred into a solution consisting of equal parts of a 10 per cent solution of formaldehyde and saturated ammonium oxalate solution. Paraffin sections were made and examined under the polariscope. Calcium granules appear in the villi of from 3 to 6 months placentas. This calcium is transport calcium destined for the child. The morphologic observations and the chemical investigations prove that the resorption of calcium by the placenta is due to the functional activity of the chorionic epithelium. The basement membrane of the epithelium acts as a semipermeable membrane. The calcium diffuses from the stroma of the villi through the delicate fetal endothelium into the blood. Calcium incrustations of the mature placenta do not possess significance for the fetal life.

W. C. HUFFER

Microbiology and Parasitology

BLOOD CULTURES AFTER TONSILLECTOMY M. I. RUBIN, I. M. EPSTEIN and M. WERNER, *Am J Dis Child* **38** 726, 1929

Blood cultures were taken from seventy-eight selected patients following tonsillectomy. All patients showed evidences of recent infections of the throat. Positive cultures were not obtained in any case.

AUTHORS' SUMMARY

THE INFECTIVITY OF ISOLATED INCLUSION BODIES OF FOWL-POX C. EUGENE WOODRUFF and ERNEST W. GOODPASTER, *Am J Path* **5** 1, 1929

The inclusion body of fowl-pox is composed of hundreds of minute bodies enclosed in a fatty capsule. The hyperplastic epithelium of the lesion of fowl-pox when subjected to tryptic digestion, liberates the intact inclusion bodies, while the epithelial cells undergo complete digestion. A single inclusion body, when washed with saline solution and inoculated into the skin of a hen, produced the typical lesion of fowl-pox containing the characteristic inclusions. The fluid in which the inclusion body is finally suspended is innocuous. The inclusion bodies of fowl-pox are interpreted as being true virus bodies, i. e., minute colonies of the etiologic agent of the disease. The proliferation of the virus is accordingly largely, if not entirely, intracellular.

AUTHORS' SUMMARY

A STUDY OF AMEBIASIS IN NEW YORK CITY LOUIS F. BISHOP and LOUIS F. BISHOP, JR., *Am J Trop Med* **9** 297, 1929

From this study of amebiasis occurring endemically in New York City, we were able to conclude that its frequency is probably greater than is commonly supposed. We were able to reach no conclusions as to the epidemiology of these endemic cases from our study, but we believe that a great deal more attention should be paid to the diagnosis of carriers of *Endameba histolytica*. More attention should be paid to the technic of microscopic examination of the feces in New York City than has been done in the past.

AUTHORS' SUMMARY

BACILLUS CALMETTE-GUÉRIN (B. C. G.) S. A. PLITOFF, ARNOLD BRANCH and WILLIAM STEENKEN, JR., *Am Rev Tuberc* **19** 9, 1929

The B. C. G. organism in undissociated form is not very virulent for guinea-pigs and rabbits. Progressive tuberculosis occurs rarely, but it does occur. There is still ignorance in regard to the complete life cycle of the tubercle bacillus.

B C G can probably be kept at a low level of virulence by cultivating it on glycerol-bile-potato medium but if it is to be used as a vaccine, one must bear in mind that the human body is not to be compared with glycerol-bile-potato as a medium for its continued viability and development. It cannot be predicted what may happen if B C G is implanted in the human body and if it is accidentally carried from human being to human being, or what transformations of it may occur. There are indications that the avirulent R (rough) organisms may be transformed into the more virulent S (smooth) ones by cultivation of the former on a medium containing their antiserum. From studies on more than 250 guinea-pigs and rabbits, it is believed that the use of B C G in prophylactic immunization may be a dangerous procedure.

H J CORPER

THE ISOLATION OF THE TUBERCLE BACILLUS FROM SPUTUM MOTI MALKANI,
Am Rev Tuberc **19** 47, 1929

Neither brilliant green, malachite green, gentian violet with basic fuchsin, with or without sodium ricinoleate, nor thymol in various concentrations, incorporated in the glycerol-egg medium, inhibits the growth of some of the contaminating micro-organisms (when planted in pure cultures) commonly present during the isolation and cultivation of the tubercle bacillus. A sediment of sputum digested with sodium hydroxide can be approximately neutralized by adding a few drops of normal hydrochloric acid. Accurate neutralization does not yield a higher percentage of growths. Hence, an indicator is not necessary. Such a procedure may decrease the incidence of contamination, but a strict bacteriologic technic is essential. Acid digestion may prevent the growth of tubercle bacilli from one sputum, while alkaline digestion prevents it from other sputums. Perhaps this can be explained in the light of recent studies on the dissociation of the tubercle bacillus. It seems that in order to get a constantly high percentage of primary isolations of tubercle bacilli from sputum, both methods of digestion and more than one medium should be employed.

H J CORPER

MADUROMYCOSIS K L PUESTOW, Arch Dermat & Syph **20** 642 1929

Maduromycosis (*Aspergillus nidulans*) involving the head and forearm of a white girl aged 19 years and a native of New York, is reported. The lesions healed under treatment.

FRANK M COCHEMS

STREPTOCOCCAL PUERPERAL INFECTION JOHN W HARRIS and J HOWARD BROWN, Bull Johns Hopkins Hosp **44** 1, 1929

Of 113 cases of streptococcal puerperal infection, 67 per cent showed streptococci of various varieties in the uterine cavity. Infection with aerobic, beta-hemolytic streptococci is almost always exogenous, while infection with gamma, nonhemolytic streptococci, in many cases is probably endogenous. Aerobic and anaerobic streptococci were found with equal frequency. Almost one half of the aerobic streptococci were of the beta-hemolytic variety, and of these most were of the pyogenes group. Relatively few mannite-fermenting streptococci were encountered.

BACTERIAL CALORIMETRY I GENERAL CONSIDERATIONS DESCRIPTION OF DIFFERENTIAL MICROCALORIMETER STANHOPE BAYNE-JONES, J Bact **17** 105, 1929

This paper describes modifications of the differential microcalorimeter of A V Hill which adapt it to study of the heat produced by growing bacteria. The chief changes are the addition of an inner vessel that can be filled with the required amount of culture fluid and sterilized. Other minor changes permit the insertion of the thermocouples without contaminating the mediums, mechanical stirring in

place of stirring by air bubbles, and the insertion of a tube for the introduction of the inoculum and the withdrawal of small samples. Data obtained from calibrations show that the apparatus is sufficiently sensitive and accurate to measure the production of approximately 6 gram calories per hour with an error of ± 1.88 per cent and the liberation of 23.68 Gram calories per hour with an error of ± 3.33 per cent in a vessel and fluid having a heat capacity equivalent to 125 cc of water. The production of heat by cultures of bacteria is within these limits in most of the mediums employed, and it is estimated that the error in the measurements within this range is approximately ± 3 per cent.

AUTHOR'S SUMMARY

BACTERIAL CALORIMETRY. II. RELATIONSHIP OF HEAT PRODUCTION TO PHASES OF GROWTH OF BACTERIA. STANHOPE BAYNE-JONES and HENRIETTA S. RHEES, *J. Bact.* **17** 123, 1929.

By means of simultaneous observations of the production of heat by bacteria and enumeration of the organisms in the culture, it is possible to correlate the curves of growth with the curves of liberation of heat. A combination of such observations with observations of the morphologic changes and other life-phases of bacteria yields some information as to the metabolic activities of a culture at various periods. By the use of Buchanan's formula, the rate of the production of heat by a single bacterial cell can be calculated, and the observed values agree closely with those derived by this calculation. Changes in the rate of the production of heat are related to changes in the rate of the growth of bacteria. Young bacterial cells produce more heat per cell than older ones. After about the fifth hour of growth, the production of heat reaches a low level and remains constant, suggesting the existence of a basal metabolic rate during that period.

AUTHORS' SUMMARY

THE SUBMANDIBULAR VIRUS OF GUINEA-PIGS. GORDON H. SCOTT, *J. Exper. Med.* **49** 229, 1929.

The development in the submandibular glands of guinea-pigs of intranuclear inclusions traceable to submandibular virus can be wholly suppressed by ligation of the gland ducts. Inclusions appear in far greater numbers in glands stimulated with pilocarpine than in ordinary spontaneous and induced infections.

AUTHOR'S SUMMARY

THE REVERSION OF R TO S PNEUMOCOCCI. HOBART A. GRIMMAN, *J. Exper. Med.* **49** 237, 1929.

A study was made of the behavior of strains of pneumococci of the R form under various experimental conditions. It was found that daughter colonies frequently appeared among pneumococci of the R form and in some instances tended to replace those of the typical R form. The daughter strain produced colonies with shiny surfaces, which were morphologically indistinguishable from colonies of genuine S pneumococci, although in characteristics, the bacteria comprising them conformed to the R variety. Both R and daughter forms that had resided for long periods of time in vivo were converted into virulent forms. Strains of R pneumococci which seemed irreversible were apparently converted into strains of S form by applying the methods of Griffith. A general consideration of the information derived during the recent experimental studies indicates that the virulent S form may dissociate into the R form in vivo, that pneumococci of the R form may occasionally be found in the sputum of patients with pneumonia and also may reside or lie dormant in vivo for a considerable period of time. It has been shown that under favorable circumstances the R form may spontaneously revert to the original S form or by special methods may even transform into an S form of another type.

AUTHOR'S SUMMARY

PNEUMOCOCCUS AUTOLYSIS WALTHER F GOEBEL and OSWALD T AVERY,
J Exper Med 49 267, 1929

Autolysis of pneumococci is accompanied by proteolysis, which results in an increase in amino and noncoagulable nitrogen. Autolysis of pneumococci is accompanied by lipolysis during which there is a liberation of ether-soluble fatty acids. When extracts containing the active intracellular enzymes are added to heat-killed pneumococci, lysis of the cells occurs and there is an increase in the non-coagulable and amino nitrogen, comparable to the changes accompanying spontaneous autolysis. When extracts containing the active intracellular enzymes are added to emulsions of the alcohol-soluble lipoids extracted from pneumococci, an increase in the ether-soluble fatty acid occurs. Sodium desoxycholate in excess inhibits the action of pneumococcus protease; it does not inhibit the action of pneumococcus lipase. When suspensions of pneumococci are cooled to 0 C, a temperature at which the rate of the action of enzymes is greatly retarded, the organisms go into solution rapidly when sodium desoxycholate is added but this process is not accompanied by lipolysis or proteolysis. It does not seem probable therefore, that the "bile" solution of pneumococci is identical with the phenomenon of autolysis as ordinarily understood and measured. The relation of the action of enzymes to antigenic dissociation is discussed.

AUTHORS' SUMMARY

A FATAL INFECTION OF CHICKS DUE TO BACILLI OF THE PARATYPHOID B
GROUP PHILIP R EDWARDS J Infect Dis 45 191, 1929

An epizootic of chicks has been observed in which the mortality was approximately 25 per cent. Two organisms of the paratyphoid B group, *Bacterium aertrycke* and *Bacterium anatum* were isolated from the chicks examined.

AUTHOR'S SUMMARY

BACTERIA ISOLATED FROM INFECTIONS OF THE NASAL CAVITIES AND MIDDLE
EAR OF RATS DEPRIVED OF VITAMIN A R G TURNER, J Infect Dis
45 208, 1929

A fatal septicemia may be produced in rabbits by organisms isolated from the suppurations of the upper respiratory tract and middle ear of albino rats suffering from lack of vitamin A. These organisms appear as gram-negative cocci by their morphology and by their fermentative powers. Apparently their poisonous effect is produced by an endotoxin and not by a toxic substance secreted by the organism. The toxicity for rabbits of gram-positive organisms (*Staphylococcus aureus*) found in the same rats compares favorably with the toxicity of known strains of *Staphylococcus aureus*. Organisms classified as Friedlander-like, except for one indol-producing strain, appear to be avirulent.

AUTHOR'S SUMMARY

CARBOHYDRATE FERMENTATION NITROGENOUS METABOLISM AND CATALASE
PRODUCTION BY VARIANTS OF BACILLUS ANTHRACIS W J NUNGESTER,
J Infect Dis 45 214, 1929

Seven colony variants of a stock strain of *Bacillus anthracis*, the two Pasteur vaccine cultures and a recently isolated strain of the anthrax bacillus were studied as to their carbohydrate fermentation, nitrogenous metabolism and catalase production. All strains produced acid from glucose, levulose, saccharose, maltose and dextrin and failed to ferment glycerol, lactose, galactose, raffinose, mannitol and inulin. Quantitative differences existed between the various strains in their proteolytic activity as evidenced by ammonia formation. These differences could not be correlated with virulence. Quantitative differences likewise existed between the various strains in their ability to decompose hydrogen peroxide. These differences could not be correlated with the virulence of the strain or with its pro-

teolytic activity. Thus while no differences were noted among the various cultures of *B. anthracis* studied with respect to their ability to ferment various carbohydrates, the limits of the ammonia and catalase production by the cultures studied were wider.

AUTHOR'S SUMMARY

DISSOCIATION OF DIPLOCOCCUS FROM MIASIS. RUTH TUNNICLIFF, J. Infect Dis 45 235, 1929

As a result of aging strains of measles diplococci, two additional culture types have been obtained. The original colony is a small, smooth colony with a wide green zone (small S), the first variant is a large, smooth, less green colony with a narrow zone of partial hemolysis (large S), these two colonies in ascites plain agar are clear and smooth with regular edges, the second variant is a large, smooth, moist, slightly green colony with no hemolysis and is smooth, opaque and slightly granular on ascites agar (large SR). All forms are gram-positive. The original coccus is small, round or slightly elongated in pairs or chains, the first and second variants are large, round in pairs and clumps, the second variant often showing a capsule. The original small S culture does not ferment salicin, the two variants ferment salicin. The three culture types vary in their phagocytability, the original type is phagocytatable, the first variant more so and the second variant generally not phagocytatable. The small S type (Duval-Hibbard) now produces no substance toxic for paramecia, the large S type is slightly toxic and the large SR is very toxic for paramecia. The toxin from the large S type is partially neutralized by antimeasles-diplococcus goat serum and the serum of patients convalescing from measles. The toxin from the large SR type is neutralized by neither. By transplanting the three types twenty-one times in anaerobic blood agar cultures at 36 C., the small S type remained the same, the large S colonies were changed to SR, and the large SR to large S colonies, but small S colonies appear in neither the large S nor the large SR cultures. By transplanting the large S and the large SR cultures frequently in dextrose broth at room temperature or at 36 C., the large S could be changed to large SR and SR to large S colonies, but only after twenty-five transfers in dextrose broth at room temperature did the large S type revert to the small, smooth colony with a wide green zone (small S).

AUTHOR'S SUMMARY

USE OF PARAMECIA FOR STUDYING TOXIC SUBSTANCES IN URINE. RUTH TUNNICLIFF, J. Infect Dis 45 244, 1929

The results of these experiments indicate that urine from patients with scarlet fever in the acute stage generally contains a toxic substance which kills paramecia and that this action is neutralized by scarlet fever antitoxin, but not by diphtheria antitoxin. A toxin substance is rarely found in the urine of patients after the administration of scarlet fever antitoxin and does not appear to be present during convalescence. A substance toxic for paramecia which could be neutralized by diphtheria antitoxin was rarely found in urine from diphtheria patients. A toxin neutralized by scarlet fever antitoxin was observed once in a diphtheria patient whose throat contained hemolytic streptococci. Urine from patients with measles showed no toxic substance which could be neutralized by scarlet fever antitoxin, anti-measles-diplococcus goat serum, normal goat serum or by serum from patients convalescing from measles.

AUTHOR'S SUMMARY

THE NATURE OF BACTERIAL RESISTANCE TO BACTERIOPHAGE. F. M. BURNET, J. Path. & Bact. 32 349, 1929

Two bacteriophage resistant strains have been produced in which no change of phase (S or R) from the parent culture has occurred. These resistant variants are serologically identical with their parent strains. With resistance there is an

associated inability to adsorb the phage concerned with retention of the power to adsorb specifically phages that are still active against the strain

AUTHOR'S SUMMARY

ANIMAL STRAINS OF HEMOLYTIC STREPTOCOCCI J SMITH, J Path & Bact 32 401, 1929

A detailed study of the cultural characteristics of a number of strains of hemolytic streptococci isolated from cows, horses and guinea-pigs has not shown a possible method of differentiating animal from human strains. The exotoxin produced by certain strains obtained from cows and horses appears to be identical with the exotoxin obtained from human strains

AUTHOR'S SUMMARY

ESCULIN FERMENTATION AND HEMOLYSIS BY ENTEROCOCCI C WEATHERALL and J H DIBBLE J Path & Bact 32 413, 1929

The ability to split esculin in bile-containing mediums is a property of the enterococci. This property is slightly more widely distributed in the enterococcus-streptococcus group than is thermoresistance which must therefore be regarded as a somewhat more specific criterion of enterococci. True hemolytic streptococci occur in the stools, but are not common. The enterococcus is typically a non-hemolytic organism, some strains when freshly isolated, show pseudohemolysis under suitable circumstances

AUTHORS' SUMMARY

THE SIGNIFICANCE OF COCCAL ORGANISMS IN EXPERIMENTAL POLIOMYELITIS R W FAIRBROTHER, J Path & Bact 32 435, 1929

Cocci have been isolated infrequently from tissues of monkeys during the different stages of the disease experimental poliomyelitis. Similar cocci have also been isolated from healthy animals, and from animals suffering from other conditions. Certain properties of the cocci have been considered. These cocci have been found to have no etiologic relationship to the disease. The cocci are members of the group of air micrococci and occur as air-borne contaminants although under certain circumstances they may be found as terminal invaders, arising probably from the nasopharynx

AUTHORS SUMMARY

THE HISTOLOGY OF EXPERIMENTAL POLIOMYELITIS E WILSON HURST, J Path & Bact 32 457 1929

Poliomyelitis is an inflammatory disease of the whole nervous system with especial involvement of the anterior horn cells, there is at present no reason forthcoming for this peculiar distribution of the most severe lesions. The nerve cells are primarily affected by the virus, and their degeneration is not attributable to the accompanying interstitial inflammation. The cellular reaction is described in detail, and the role played by polymorphonuclear leukocytes and by the microglia emphasized. The various stages of evolution of the latter correspond to the "polyblasts, 'elongated glial cells,' etc., of the older authors. Meningitis is not a necessary feature of the disease and is often not marked in the early stages. The hemorrhages seen with some frequency result, at least in some cases, from slight trauma at autopsy to the greatly congested vessels

AUTHOR'S SUMMARY

BACTERIOLOGIC STUDIES OF THE UTERINE CAVITY OF PREGNANCY FRIEDHEIM ISBRUCH, Arch f Gynak 135 108, 1928

Isbruch's conclusions were based on bacteriologic studies of twenty-four women in pregnancies ranging from early to full term and six dogs at full term the young of which were delivered through abdominal incisions. Cultures were made from the amniotic waters and from sections of placenta and decidua. The author

found that the uterine cavity was sterile during pregnancy. However, he stated that after prolonged labor and after a long period of ruptured membranes, the uterine cavity did contain organisms that extended upward from the vagina. The author conceded also that organisms, pathogenic or potentially so, might be found in the uterine cavity with relatively short labor or with recently ruptured membranes. These organisms, however, did not always call forth a reaction on the part of the patient. Isbruch did not believe that there is a latent endometritis.

A. J. KOBAR

THE INHIBITIVE AND DESTRUCTIVE ACTIONS OF THE ANILINE DYES. H. STUDEMANN, Arch f Ophth 122 572, 1929

This investigation follows up the prewar work of Romer, Gebb and Lohlem on the action of aniline dyes on germs which are pathogenic for the eye, used during the war in surgical procedures by E. Hoffmann. The author's object is to amplify the results already obtained by including organisms not heretofore subjected to this test. The more active ones of the basic dyes were used: brilliant green, iodine green, gentian violet, Hoffmann's violet, malachite green, methylene violet, methyl green, saffron T, methylene blue (methylthionine chloride, U. S. P.), methyl violet, as well as the Greifswald mixture. In a test for the purity of the individual dyes, brilliant green, malachite green and methylene blue ranked first. The remainder contained varying amounts of dextrin, especially gentian violet, which, however, would not affect their action on the eye. In this regard the combination with zinc chloride in the case of methyl green should rather be considered. The effect of these dyes (in various concentrations) was tested on three strains each of *Bacillus typhosus*, *Bacillus coli* and the anthrax bacillus, and on two strains each of Koch-Weeks' bacillus and one each of *Bacillus diphtheriae* and *Bacillus pyocyaneus*; all of them in vitro, the maximum period of exposure was twenty minutes. Two strains of *Bacillus anthracis* only were tested on white mice.

Malachite green and brilliant green have the strongest effect on the growth of *B. typhosus*, *B. coli* and *B. pyocyaneus* strains, for the last-named they alone are effective. The Koch-Weeks strains were unaffected by any of the dyes. For *B. diphtheriae* malachite green, gentian violet, methyl violet, Greifswald mixture, brilliant green, Hoffmann violet, methylene violet, methylene blue and saffron T were effective, in the order given, for *B. anthracis* brilliant green, malachite green, gentian violet, methyl violet, Greifswald mixture, Hoffmann violet, methylene violet, saffron T, methyl green, and for streptothrix strains malachite green, Greifswald mixture, brilliant green, methylene violet, gentian violet, methyl violet and Hoffmann violet. Of aspergillus, *Aspergillus niger* was most affected and that by the Greifswald mixture, methyl violet, gentian violet, Hoffmann violet, methylene violet, malachite green, brilliant green and methyl green, in the order named. *Aspergillus fumigatus* was next, affected by methyl violet, the Greifswald mixture, gentian violet, malachite green, brilliant green, methylene violet and methyl green. *Aspergillus flavus* was destroyed by none of the dyes. After forty-eight hours every one of the dyes in even the lowest concentration used destroyed the anthrax bacillus. The results obtained from experimentation on white mice, using anthrax strains, make it seem justifiable to employ brilliant green, for example, in anthrax diseases of the lids, or, if toxic effects must be avoided, the next most effective dye for anthrax is gentian violet. Hoffmann violet and gentian violet in concentration of 1:50 were nontoxic for all animals, all the other dyes in this concentration and the undiluted Greifswald mixture were toxic.

CHARLES WEISS

TUBERCULOUS RE-INFECTIONS OF THE LUNG. L. ASCHOFF, Klin Wchnschr 8 1, 1929

By re-infection of the lung is understood every new tuberculous infection from some extrapulmonic focus whether hematogenous or aerogenous. All isolated

reinfections start, according to their pathologic anatomy, with a stimulus productive of exudation, from which, as a rule, with marked resorption of the exudate, the scar stage (cartilagenous pleural scars, subpleural scars, intrapulmonic scars with or without caseocalcareous deposits) develops. According to the statistics of all pathologists, most of the reinfections heal. To such reinfections belong also thickenings in the pleural lymph nodes. Circumscribed indurations of the pleura and lungs, with few exceptions, are to be considered as specific tuberculous scars. All these small scars taken into account mean that the area of reinfection in the adult is as large as primary infection (90 per cent).

AUTHOR'S SUMMARY

THE TRANSMISSION OF *B. MURIS RATTI* TO WHITE MICE V SCHILLING,
Klin Wchnschr 8 55, 1929

The infection of the rats with *Bartonella* extended over a long period. Infection of the histiocyte giant cells of the bone-marrow and the production of methemoglobin within the body were demonstrated. Transmission of the infection occurred with eight of thirteen mice to a slight degree, and with all of eleven splenectomized mice to a marked degree. All mice developed the disease after splenectomy. Only the splenectomized mice died. The influence of the spleen in susceptibility was unquestionable.

AUTHOR'S SUMMARY

THE TIME OF THE PENETRATION OF TUBERCLE BACILLI INTO THE REGIONAL LYMPH GLANDS AND BLOOD STREAM OF GUINEA-PIGS AFTER CUTANEOUS INOCULATION H MARTENSTEIN, Klin Wchnschr 8 159, 1929

In experimental tuberculosis of the guinea-pig (infective dose 0.01 mg), the tubercle bacilli penetrated at once into the regional lymph glands following inoculation into scarified skin, and somewhat more slowly, that is, within from 1 to 2 hours, following intradermal inoculation. Tubercle bacilli were not demonstrated in the heart's blood.

AUTHOR'S SUMMARY

AVIAN TUBERCULOSIS IN MAN E LOWENSTEIN, Med Klin 24 1782, 1928

In man, avian tuberculosis begins as a sepsis with fever that may last a long time. Later, foci develop in the marrow, kidneys, skin and spleen. The diagnosis depends on the demonstration of the avian bacillus. Infected persons react to the avian tuberculin, while patients with mammalian tuberculosis do not.

THE YELLOW FEVER SPIROCHETE OF NOGUCHI IN HUMAN TISSUES (AFRICAN YELLOW FEVER) W H HOFFMANN and F JAHNEL, Munchen med Wchnschr 75 2131, 1928

In preparations of the liver, kidneys, lungs, heart and stomach, stained according to the old and the new methods of Levaditi, structures resembling *Leptospira* were not found.

AUTHORS' SUMMARY

GLANDERS-LIKE PYEMIA IN A BREAST-FED NEW-BORN CHILD ALFRED PLAUT,
Virchows Arch f path Anat 270 672, 1929

A normally delivered, mature infant of a healthy primipara became sick at the end of the first week. The temperature was 104 F, with green liquid stools, swelling of the abdomen and finally vomiting. Death occurred on the eighteenth day of life. The liver and spleen were found studded with irregularly distributed, spherical, well outlined, yellowish-green foci, averaging in size between that of a rice grain and that of a pepper seed. One such focus was found in one kidney, and larger, less regular nodules in a lung, confluent foci diffusely involved the cecum and appendix, necrosing colitis was found in the colon ascendens, there

was diffuse serofibrinous peritonitis and pleuritis the abdominal lymph nodes were partly supplanted by such foci, the lymph nodes at the porta hepatis were intact, the umbilical vessels were partly thrombosed, but otherwise were unchanged. The microscopic examination showed necroses with thick masses of bacilli at the periphery. The bacilli were gram-negative, short, straight or banana-shaped and resistant to any staining, only the poles and the periphery taking the stain well. Their dense, inextricable masses closely imitated mycelium. They filled the blood vessels. The reaction of the tissue surrounding the foci extended through a narrow zone only. The diffuse colitis was the result of confluent hematogenous foci. The foci in the lung were larger and less regular in shape, the bronchi were secondarily affected. The thymus and suprarenal glands were small. The skull and the organs of the neck were not examined.

Cultures from heart blood, exudates and spleen yielded *Bacterium coli*, non-pathogenic for guinea-pigs (fed and injected). The colon bacillus was not identical with the organism in the lesions. Incubation of a piece from liver in broth for ten hours did not lead to an increase in the number of bacilli within the tissue.

The source of the infection, the point of its entry and the character of the organism are unknown. The main seat of infection was the colon. Four photographs demonstrate the similarity with glanders.

ALFRED PLAUT

IS THE PRODUCTION OF PATHOGENIC PROPERTIES IN SAPROPHYTIC STAPHYLOCOCCI POSSIBLE BY MEANS OF GEISSE'S METHOD? B. KEMKES, *Ztschr. f. Hyg. u. Infektionskrankh.* **109** 354, 1928

Kemkes was unable to transform saprophytic staphylococci into pathogenic forms by means of Geisse's method, which consists in repeated passage of the nonpathogenic staphylococci in collodium sacs through the peritoneal cavities of rabbits.

W. OPHULS

PANCREAS AND BACTERIOPHAGIC ACTION. E. KLHAMBICKER, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **56** 32, 1928

Bacteriophages are normally never present in sterile organs (pancreas of hog and thymus of calf). Bacteriophages can be regularly obtained from nonsterile organs of slaughtered animals. Bacteriophages are ubiquitous in slaughterhouses owing to contamination with intestinal contents. Bacteriophages can be demonstrated in the small intestine in 50 per cent of the hogs slaughtered. Sterile, raw, chopped pancreatic tissue added to bacteriophage-containing bouillon cultures hastens considerably the production of bacteriophages. Thymus acts in a similar manner. Blood tissue has a lessened effect. The causative mechanism is unknown, it does not depend on the specific pancreatic ferments nor on the action of bacteria cultured from nonsterile glands. The optimal method of producing bacteriophages is as follows: A dilution of nonsterile intestinal content in bouillon is seeded with a large amount of a lyso-sensitive strain after the addition of raw pancreas or thymus. After incubation at 37 C, the culture is filtered through Chamberland filters and tested for the lytic substance with the strain used.

WILLIAM C. HUEPER

EXPERIMENTS ON THE FILTERABILITY OF THE TUBERCULOSIS VIRUS. F. KELIER and R. WIRTHMAR, *Ztschr. f. Tuberk.* **54** 22, 1929

Pure broth cultures of tubercle bacilli and bacilliferous sputums were filtered through Chamberland filters L₂ and L₁. In spite of careful search, no acid-fast elements were ever detected in these filtrates; their cultures on optimal mediums remained sterile. In a number of series, 154 guinea-pigs were inoculated with not less than 10 cc of these filtrates, either subcutaneously or intraperitoneally. Six of the 154 animals given injections yielded positive results. Three guinea-pigs developed a typical tuberculosis, two a strictly localized lesion, and con-

tained acid-fast rods in an enlarged gland, which on inoculation into two guinea-pigs produced typical tuberculosis. Five animals showed a moderately positive intracutaneous tuberculin reaction, but they showed no lesions at autopsy. Search for acid-fast elements in the lymph glands of injected animals was unsuccessful, with the exception of the six animals mentioned. It is concluded that the six positive results were caused by some few individual bacteria of decreased virulence having passed the filter, accidentally as it were. The control of the retentive power of bacterial filters by other bacterial strains (which was employed in these experiments) is unreliable. The positive results do not prove the existence of a "filtrable virus." If it existed, it should be possible to demonstrate its presence regularly or at least much more frequently.

MAX PINKER

Immunology

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI J. M. NEILL, W. L. FLEMING and A. L. HARRIS, *Am J Hyg* **10** 1, 1929

The paper presented two examples of the range of reacting specificity on the immediate skin reaction type of hypersensitiveness to the diphtheria-diphtheroid group of bacteria. Persons reactive with diphtheria bacilli were also reactive with many nontoxicogenic diphtheroids of diverse origin and of different fermentative properties. These examples showed that the reacting range of hypersensitiveness of a person can embrace a wide variety of strains of the diphtheria-diphtheroid group. It is probable that the subjects had been sensitized by one kind of bacteria and that the responses to the other strains were due to the immunologic relationship (not identity) to the sensitizing strain, i. e., that the hypersensitive reactions, while not strain-specific, were immunologically specific and dependent on similar group antigens among the different diphtheroids.

The results suggest that hypersensitive reactions may be given to the subsequent injection of diphtheria bacterial material by persons previously sensitized against certain diphtheroids, conversely that hypersensitive reactions may be given to certain diphtheroids by persons originally sensitized by diphtheria bacteria.

AUTHORS' SUMMARY

SEASONAL VARIATION OF DIPHTHERIA ANTITOXIN CONTENT OF THE BLOOD OF ADULTS AND ADOLESCENTS R. G. PERKINS, R. H. HELREN, E. MEGRAIL and A. B. GROSSMAN, *Am J Hyg* **10** 13, 1929

A study has been made of the diphtheria antitoxin content of the blood in a group of school boys from 11 to 14 years of age and in adults.

A low content has been shown in the late winter and in the spring in the boys, whereas the adults whose occupations place them under conditions of exposure not too dissimilar present an entirely different picture.

This work confirms Fitzgerald's observations in demonstrating the existence of adults with practically no antitoxin in the blood, and shows also that there may be a certain number of adolescents with similar characteristics.

The authors believe that the investigation strengthens the probability that the fundamental factor in seasonal variation in diphtheria is a modification of the resistance of the individual at the actual portal of entry.

JOHN PHAIR

RESPIRATORY IMMUNITY IN RABBITS C. G. BULL and C. M. MCKEE, *Am J Hyg* **10** 229, 1929

Rabbits which have been immunized with pneumococcus types II, III or IV are completely resistant to intranasal infection with type I organisms and also manifest considerable resistance to intravenous infection with the same types.

AUTHORS' SUMMARY

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI J M NEILL, L V RICHARDSON, A L HARRIS, W L FILMING and J Y SUGG, *Am J Hyg* **10** 551, 1929

Hypersensitive immediate skin reactions may be given in response to two different products of diphtheria bacilli a relatively stable (80 C) substance contained in filtrates of either nontoxigenic or toxigenic strains, and a labile (60 C) substance contained only in filtrates of toxigenic strains. The tests on a previous group of adults were made with heated filtrate alone and hence did not reveal those reactive with the labile bacterial product. For this reason, a new group of adults was tested with unheated as well as with heated filtrate. Thirteen of the 2,150 persons, or 0.6 per cent of the group, gave significant hypersensitive immediate skin reactions to the diphtheria bacterial substances. The test group included white persons and negroes, and adult students and outpatients of the hospital dispensary.

AUTHORS' SUMMARY

SEROLOGICAL DIFFERENTIATION OF STERIC ISOMERS (ANTIGENS CONTAINING TARTARIC ACIDS) K LANDSTÄMNER and J VAN DER SCHEER, *J Exper Med* **50** 407, 1929

In continuation of studies on the stereochemical specificity of serum reactions, antigens were examined containing the acyl radicals of the levotartaric dextro-tartaric and mesotartaric acids. It was found that in this case also, immune serums can readily be obtained which differentiate sharply the three antigens which are identical in every other respect but possess stereoisomeric groups. Since the tartaric acids by their chemical constitution belong to the same class of substances as sugar acids the results have a bearing on the question of the specificity of natural antigens containing carbohydrates such as have been described by Avery and Heidelberger.

AUTHORS' SUMMARY

THE ANTIBODY-FORMATION BY POLYSACCHARIDS SHOJI NISHIMURA, *J Exper Med* **50** 419, 1929

It has been clearly demonstrated by complement-fixation tests that the serums of rabbits immunized with mulin, soluble starch and dextrin contain specific antibodies. All these immune serums gave a negative precipitation reaction. The kind of dextrin which has a construction very near to starch has an antigenic property, but those in a state of further decomposition do not give rise to antibodies. All the three kinds of polysaccharids have the power to produce antibodies without any vehicle. Dextrin is the only one of the three that gives rise to immune bodies more readily when pig serum is added to it. Regarded as antigens, mulin stood first and soluble starch and dextrin next in order. All three kinds of polysaccharids that were employed gave a negative protein color reaction. All of them, however, contained nitrogen. It has been proved that the large portion of the nitrogen contained in the soluble starch is derived from its protein contents. It is suggested that in the production of immune bodies by these three kinds of polysaccharids, proteins might play the part of the vehicle. This is, however, still to be determined.

AUTHOR'S SUMMARY

THE ANTIBODY RESPONSE IN THE HUMAN BEING AFTER INJECTION WITH NORMAL HORSE SERUM LOUIS TURT and S G RAMSDALL, *J Exper Med* **50** 431, 1929

After the injection of normal horse serum in the human being, serum sickness occurs even more regularly than in patients treated with the various immune serums, but this is not accompanied by the production, to any notable degree, of circulating antibodies of the various types that are regularly to be demonstrated after the administration of immune serum and its resulting serum sickness. Since

normal horse serum therefore appears to be weakly antigenic, and immune serum highly antigenic for the human being, one must assume that this difference is the result of some alteration in its antigenic characteristics produced during the course of the immunization or of its preparation for use, or that the specific antibody which is responsible for the phenomenon of serum sickness has not yet been identified, or that this phenomenon is not in any way dependent on the presence of the various known antibodies to normal horse serum

AUTHORS' SUMMARY

ANTIBODY AND AGGLUTININ IN PNEUMOCOCCUS PNEUMONIA F T LORD and G E NESCHE, *J Exper Med* 50 449, 1929

Protective substances and agglutinins were not demonstrated in the blood of patients with pneumonia untreated with serum before the fall in the temperature by crises or lysis. Protective substances and agglutinins were frequently demonstrated in serum-treated patients during the course of the disease. Protective substances and agglutinins were usually present at the time of the temperature fall in patients untreated with serum and persisted for days or weeks thereafter. Protective substances have an important bearing on the outcome. A large proportion of those with protection recover and a large proportion without it die. Agglutinin and antibody may appear simultaneously or one may precede or be present without the other. Tests for agglutinin are unreliable as a control of dosage of specific serum.

AUTHORS' SUMMARY

SKIN TESTS WITH FILTRATES AND VACCINES OF STAPHYLOCOCCUS AUREUS M L AFREMOW and I PILOT, *J Infect Dis* 45 167, 1929

In a group of 1,062 persons without obvious staphylococcus infection 417 (47 per cent) gave positive reactions after the intradermal injection of diluted filtrate. In a group of 56 patients suffering from acute or chronic infections with *Staphylococcus aureus*, 49 (89 per cent) reacted positively. Of 41 patients with diabetes, 21 (52 per cent) reacted positively. Intradermal tests with vaccine on 236 persons without obvious staphylococcic infection gave 117 (46 per cent) positive reactions. Patients infected with *Staphylococcus aureus* in a series of 36 cases gave 33 (89 per cent) positive reactions with vaccines. Individual immunity to *Staphylococcus aureus* as determined by skin tests may be influenced by intramuscular injections of filtrate or vaccine. Antitoxic rabbit and horse serums, and serum obtained from persons giving negative skin reactions neutralize the filtrates in certain dilutions.

AUTHORS' SUMMARY

PREPARALYTIC POLIOMYELITIS. TREATMENT WITH CONVALESCENT SERUM W L AYLCOCK, E H LUTHER, C F MCKHANN, E C SMITH and S D KRAMER, *J Infect Dis* 45 175, 1929

One hundred sixteen patients with preparalytic poliomyelitis were treated with the serum of persons convalescing from poliomyelitis. The outcome in these cases, as measured by case fatality rate, percentage of cases which developed no paralysis, percentage of cases which developed paralysis of the two severe grades as well as by the average amount of paralysis per case is strikingly different from the outcome in untreated patients in the same outbreak. That this difference is not due in any great degree to the inclusion of patients with milder forms of the disease, which are ordinarily missed, among the treated patients by reason of diagnosis, is indicated by the close correspondence between the results in the state at large and in Watertown-Waltham, where there were increased opportunities for detecting milder forms of the disease and where a larger number of the patients were seen and treated. A relatively enormous number of missed cases must be assumed to have occurred in order to equalize the outcome in treated and untreated patients. A house-to-house canvass in one locality in which the disease

was prevalent failed to disclose the occurrence of any number of missed cases. All treated patients presented typical signs and symptoms of preparalytic poliomyelitis. The subsequent occurrence of some paralysis in 61.2 per cent of the treated patients indicates that we were not dealing largely with a nonparalytic form of the disease. Twenty-three per cent of the cases in which no paralysis developed were of the so-called dromedary type as compared with 26.8 per cent of the cases in which paralysis developed. As the dromedary phenomenon is peculiar to poliomyelitis, this is regarded as an additional substantiation of the diagnosis in the group of cases in which no paralysis developed. Of 143 patients observed for suspected preparalytic poliomyelitis, who were excluded the majority subsequently were found to be suffering from other conditions. In only eight cases could the suggestion of abortive (not preparalytic) poliomyelitis be considered.

AUTHORS' SUMMARY

PREPARATION OF MENINGOCOCCUS TOXIC SUBSTANCES NECESSARY FOR PHENOMENON OF LOCAL SKIN REACTIVITY. GREGORY SHWARTZMAN, J. Infect Dis 45 232, 1929

Work reported in this paper was done with filtrates of washings of meningococcus growth on 0.7 per cent glucose agar from twenty to twenty-two hours old. Of 74 surviving rabbits in which attempts were made to elicit the phenomenon with the use of this filtrate, 73 (98.6 per cent) showed severe hemorrhagic necrotic reactions. The smallest amount of filtrate necessary to inject intradermally was 0.025 cc. As little as 0.1 cc of undiluted filtrate per kilogram of body weight injected intravenously was sufficient to elicit severe local hemorrhagic necrosis. (Smaller amounts were not tested.) The primary erythema produced by the injections of these filtrates was insignificant. There was a high general toxicity of these filtrates since doses even as small as 0.1 cc per kilogram of body weight injected intravenously killed a certain percentage of rabbits.

AUTHOR'S SUMMARY

DIAGNOSTIC VALUE OF THE "VACCINIA VARIOLA" FLOCCULATION TEST. W. L. BURGESS, JAMES CRAIGIE and W. J. TULLOCH, Medical Research Council Special Report Series No 143, 1929

From the examination of ninety-six specimens of crusts from ninety-three cases of smallpox, chickenpox, vaccinia and other conditions, it is seen that the vaccinia flocculation test gives specific reactions of diagnostic value. The fact that the material on which these tests were carried out has been derived from different outbreaks of chickenpox and smallpox, separated in both point of time and geographical distribution and in the case of vaccinia obtained from different animal species, renders it improbable indeed that the flocculation was due to interaction of adventitious antibodies in the antiserum with secondarily invading organisms or their products in the test antigens. Experiments in which vaccinia flocculating serum was absorbed with staphylococci obtained from vaccinia crusts, and subsequently tested by extracts of the same crusts also indicate that the reaction is not due to the presence of secondarily invading micro-organisms.

The discussion of the mechanism of the reaction permits of but two hypotheses being advanced to explain its occurrence: (a) that a union of antigen (vaccinia or variola) with true antibodies to the virus is formed and that the floccules which appear are due to the union [the floccules may be rendered more easily demonstrable by entanglement of epithelial debris to which the virus adheres] and (b) that the reaction may be due to the development of heterophil qualities in the epithelium of different animal species infected with the same virus, and may therefore to some extent, resemble the Wassermann reaction.

Without committing ourselves to an expression of opinion as to which of these two possibilities offers the true explanation of the facts observed, it appears to

us that for the time being it would be well to accept the first as a working hypothesis

AUTHORS' SUMMARY

THE IMMUNIZING DOSE OF VACCINIA PETER A. CLEARKIN, Brit J Exper Path **10** 237, 1929

Very small quantities of vaccinia virus protect against enormous doses. Before standardization of vaccine lymph becomes feasible it must be prepared in a more stable form.

AUTHORS' SUMMARY

THE ACTION OF AMMONIA ON COMPLEMENT I. GORDON and P. G. MARSHALL, Brit J Exper Path **10** 249, 1929

From the results obtained, it would appear that inactivation of complement by ammonia, i. e., destruction of the fourth component, was not associated with any interference with the protein constituents of serum or with any interference with the phosphorus partition.

AUTHORS' SUMMARY

THE PASSAGE OF ANTIBODIES INTO THE INTRA-OCULAR FLUIDS AND THE CEREBROSPINAL FLUID AND THE EFFECT OF THEOPHYLLINE UPON IT A. FRANCESCHETTI and C. HALLAUER, Arch f Augenh **100-101** 59, 1929

The breaking down of the aqueous humour barrier by means of theophylline in actively immunized rabbits also leads to an increased transition of agglutinins into the aqueous humour.

The agglutinin titer of the fluids of the anterior chamber is greatly increased after the administration of theophylline. Similarly, after passive immunization, the passage of agglutinins into the aqueous humour is increased by theophylline.

The permeability of the aqueous humour for hemolytic amboceptors is increased by the administration of diuretics, the actual increase being the same as for agglutinins.

Although it is scarcely possible to demonstrate precipitins in the normal aqueous humour of immunized rabbits a constant distinct precipitate appears after the use of theophylline, particularly if double the amount of aqueous humour is used in the test.

Hemolytic amboceptors which in normal conditions are rarely found in the vitreous humour, are present in increased quantities after injection of theophylline.

An increased passage of immune bodies into the cerebrospinal fluid could not be demonstrated as the result of the use of theophylline.

CHARLES WEISS

THE INFLUENCE OF ANTIRABIES INOCULATION ON THE DEVELOPMENT OF THE NEGRI BODIES F. GERIACH and F. SCHWEINBURG, Zentralbl f Bakteriol **110** 159, 1929

The investigations of the authors led them to conclude that Negri bodies or the Babes-Koch-Rising granulations are not degeneration products, but are really structures of a parasitic nature. In cases of rabies negative to Negri bodies they could regularly demonstrate the latter granules, and they believe that these probably develop into the Negri bodies.

PAUL R. CANNON

UNDULANT FEVER IN THE PROVINCE OF BRANDENBURG W. SILBERSTEIN, Deutsche med Wchnschr **55** 1306, 1929

Agglutination reactions for *B. abortus* carried out on 469 samples of blood received in the laboratory for typhoid or paratyphoid agglutination tests disclosed nine serums which gave strongly positive reactions with *B. abortus*.

PAUL J. BRESLICH

ENCEPHALITIS AFTER SMALLPOX VACCINATION H G HUBER, Deutsche med Wchnschr **55** 1370, 1929

Three instances of disease of the central nervous system following vaccination against smallpox are described. In one instance in which symptoms were first noted on the fifth day after vaccination, the spinal fluid was found to contain vaccine virus by corneal inoculation into rabbits. In the other patients in whom symptoms did not appear until the twentieth day, no virus was demonstrated in the spinal fluid.

PAL J BRLSICH

SENSITIZATION FROM REPEATED TRANSFUSION OF PATERNAL BLOOD OF THE SAME GROUP P GEORGI and E WIFLSKY, Munchen med Wchnschr **76** 195, 1929

On account of acute anemia a child of group O, 8 years old, was given several transfusions of citrated blood, the father, also of group O, serving as one of the donors. During a transfusion with the paternal blood, a typical anaphylactic shock developed from which recovery took place. The other transfusions with blood of group O, including blood from the mother, did not give rise to any unpleasant symptoms. No agglutinins or precipitins for the blood of the father could be demonstrated in the blood of the child, but mixtures of the serum of the father and the child gave complement fixation. Mixture of the serum of the mother and the child did not give complement fixation. It is also noteworthy that the intradermal injection in the child of 0.1 ccm of the serum of the father gave a definite reaction. Such reactions were not obtained with the blood of the mother or of the child itself.

IMMUNIZATION OF CATTLE AND SHEEP BY MEANS OF BCG B LANGE and R WETHMAR, Ztschr f Hyg u Infektionskrankh **110** 465, 1929

The authors state that in their experimental animals the oral and subcutaneous administration of large doses of BCG was never followed by progressive tuberculosis. The subcutaneous introduction caused a stronger and more lasting hypersensitiveness to tuberculin than the feeding of large amounts of bacilli. The specific hypersensitiveness is not necessarily associated with an increased resistance to infection. After oral administration the animals were not sufficiently protected even against intravenous inoculation with a very weak virus. The subcutaneous treatment also was insufficient in part of the animals in spite of a relatively weak test infection. In the majority of the animals the treatment was successful to some extent. Two of three calves and four of six sheep overcame the intravenous mild infection which for control animals was surely fatal. These animals, however, were not free from tuberculosis. When they were slaughtered in good general condition several months later they all had limited but still active lesions. When a more virulent intravenous test infection was used the animals did not show any specific protection. It is evident that in cattle and sheep the protection possible by means of BCG is limited, in fact, the authors show that it is appreciably less than after intravenous injection of human tubercle bacilli.

W OPHULS

Tumors

INTRACRANIAL CHORDOBLASTOMA PERCIVAL BAILEY and DUMITRI BAGDASAR, Am J Path **5** 439, 1929

These tumors are almost invariably described as having a grossly nodular but smooth surface of a milky-white color. The cut surface is semitranslucent, resembling that of cartilage, but is softer, often jelly-like. There are cysts filled with a slimy material resembling mucus. Other tumors are described as

reddish or brownish, probably owing to interstitial hemorrhage, although they are usually poorly vascularized and bleed only slightly when incised. These growths arise in the base of the sphenoidal bone and may project either upward into the intracranial cavity from the clivus blumenbachii or downward into the nasopharynx through the craniopharyngeal foramen. In several cases there was both an intracranial and an intrapharyngeal extension. There are a few cases recorded in which the tumor seems to have been confined to the nasopharynx, but in two of these there is no record of a neurologic examination and in no instance has the absence of intracranial extension been proved by necropsy. The tumor may extend into the sphenoidal sinuses, the orbits of the eyes or even into the neck and regional veins. The microscopic appearance of these tumors is remarkably uniform. The most characteristic feature is of course, the vacuolated or physaliform cells. It has been abundantly proved that the vacuoles are filled with glycogen. Since its demonstration demands fixation of the tissue in absolute alcohol, we were unable to find it in our material. But we were able to show the presence of intercellular mucin, abundant in case 1, less so in case 2. Sometimes the cells are widely separated by the mucin, causing a superficial resemblance to a chondroma, in others, they are so closely packed that the tumor resembles a small-celled carcinoma. The cells are usually arranged in groups or cords. The nature of the nuclear vacuolization, which was frequently seen in the tumor in our case 2, is still disputed. These vacuoles are said also to contain glycogen.

AUTHORS' COMMENT

TISSUE CULTURE STUDIES OF THE GLIOBLASTOMA MULTIFORME R. C. BUCKLEY, *Am J Path* 5 467, 1929

Tissue culture preparations of ten intracranial gliomas removed at operation were made. The clinical histories and the gross structures of these tumors as seen at operation resembled previously verified examples of glioblastoma multiforme. The cultures of five of these tumors showed excellent and uniformly similar growths. The cultures of the other five tumors presented none or very little growth. The histologic structure seen in the paraffin sections of the tumor tissue from which a growth was obtained was interpreted as similar to that of the glioblastoma multiforme. A different structure in the other five tumors made the diagnosis difficult. They were interpreted as a rapidly growing glioma with cells differentiating into astrocytes. There was noted a striking similarity in the resemblance of the growing cells to those seen in fresh smears and stained paraffin sections of the same tumor tissue.

AUTHOR'S SUMMARY

THE OCCURRENCE OF MITOSES IN NORMAL AND MALIGNANT TISSUES IN VITRO ALBERT FISCHER and RAYMOND C. PARKER, *Brit J Exper Path* 10 312, 1929

The percentage of cells in mitosis was determined for fixed cultures of normal (fibroblasts) and malignant (carcinoma) tissue which had been cut in serial sections. The percentage of cells in mitosis in malignant tissue was found to exceed greatly the corresponding percentage in normal tissue, in spite of the fact that the growth-rate of normal tissue may exceed that of malignant tissue by 700 per cent. In cultures of normal tissue, the greatest number of dividing cells are to be found in the marginal areas. In cultures of malignant tissue, there is no appreciable difference between the number of dividing cells to be found in central and marginal regions. The degenerative phenomena occurring in cultures of malignant tissue have been described and suggestions made as to their significance.

AUTHORS' SUMMARY

ON EXPERIMENTAL CARCINOGENESIS THE LOCAL RESISTANCE OF THE SKIN
TO THE DEVELOPMENT OF MALIGNANCY W. CRAWER, Brit J Exper Path
10 335, 1929

Experiments are reported which show that when large areas of the skin of mice are subjected to chronic irritation by tar painting, the development of malignancy is confined to a small portion of that area. Any benign growths present tend to remain such, as long as the malignant tumor persists. On removing the malignant growth, however, any one of the benign growths may become malignant or an entirely new malignant process may develop in the remainder of the painted area. Removal of the second malignant growth has sometimes been followed by the appearance of a third malignant tumor. In fourteen mice in which cautery was applied to the base of a papilloma malignant changes were noted in six animals within five weeks. It is believed that these observations taken together suggest that the development of carcinoma is not dependent on changes in the epithelial cells alone but also on local inhibitory factors in the other tissues.

J. N. PATTERSON

PROCESSES OF DEHYDROGENATION IN NORMAL AND NEOPLASTIC TISSUES LUIGI
BARELLI, Tumori 15 533, 1929

The author's study of the phenomena of dehydrogenation by means of meta-dinitrobenzene shows a less regular behavior with rat carcinoma tissue than with normal tissue. While Pentimalli demonstrated that blood serum exerts an activating action on dehydrogenation of tissues, the author has shown that a similar effect is exhibited by cerebrospinal fluid, milk, amniotic fluid, transudates, serum (fresh as well as boiled) and even distilled water, but that this action is marked with normal tissues, and inconstant or absent with the adenocarcinoma of the rat.

W. OPHULS

ON THE TRANSMISSION OF NEOPLASMS BY ORGANS OF ANIMALS WITH IMPLANTATION TUMORS T. ANARDI, Tumori 15 561, 1929

In conformity with previous investigators, the author finds that by subcutaneous inoculation of pulp of various apparently intact organs of animals with implantation tumors, tumor formation can be produced in healthy animals of the same species. In his experiments he used rats inoculated with the adenocarcinoma type Ehrlich. Subcutaneous injection of heart blood and the inoculation of pulp of various organs of these animals caused the production of tumors in different percentages as follows: lung, 33 per cent, liver, 26 per cent, testicle, 13 per cent, spleen, 7 per cent, and blood, 4 per cent. The tumors were all of the same structure as the implanted ones. When the cellular elements in the injected materials were destroyed by mechanical, chemical, physical or biologic means which might have left a cancer producing virus intact, the results were always negative. The author concludes that the development of the tumors must be ascribed to tumor cells which were present in the circulation and in the organs of the animals with implanted tumors.

W. OPHULS

CARCINOMA OF LUNG OF TIGER DUE TO PARAGONIMUS WESTERMANII P.
COHRS, Beitr z path Anat u z allg Path 81 101, 1928

Cohrs briefly reviews the literature relating to the occurrence of the lung fluke, *Paragonimus westermani*, in the tiger, in the lung of which the parasite was first discovered in 1878, in the dog, cat, hog and man. He reports a case of squamous cell epithelioma of the lung in a tiger caused by the parasite. The primary tumor measured 4 by 4.8 cm on its cut surface. Near it was a smaller metastatic nodule, and metastases were present in the bronchial and periportal lymph nodes and in the spleen. In the smaller bronchi were numerous cystic dilata-

tions caused by the parasite. In these, metaplasia of cylindric to squamous epithelium was evident, growth of the latter into the surrounding stroma could be seen. The animal had been in captivity for sixteen years. The author believes that the infestation occurred before this time and that it led to chronic inflammatory changes in the smaller bronchi, with metaplasia of the epithelium, the latter finally taking on malignant characteristics. In the duodenum of the animal were inflammatory nodules which contained the hookworm, *Gaioncus pernicius*.

O T SCHULTZ

THE RELATION BETWEEN NORMAL AND MALIGNANT TISSUES. A FISCHER, H LASER and H MAYER, *Ztschr f Krebsforsch* 29 270, 1929

A study of the relationships between cancerous and normal tissues in vitro showed that the latter had a distinctly stimulating effect on the former, lasting as long as three weeks. The intensity of this stimulation gradually lessened. It could be separated into two phases: the first shown before the two tissues were in actual contact and due to the presence of diffusible substances, the second after direct contact was established, and due to the direct passage of material from cell to cell. On normal tissues the first effect was stimulation to connective tissue overgrowth, followed by degeneration and death. The character of the normal tissue, and even its source, was a matter of indifference, since homologous and heterologous tissues behaved alike. Of greater importance was the state of the normal tissue, the least effect being shown by those that were already killed at the time of the addition. Fresh and degenerating tissues behaved almost alike, but in any case fresh tissues degenerated rapidly. Eventually the normal tissues were completely killed and utilized by the growing tumor cells.

H E EGGERS

THE HISTOLOGIC SIGNIFICANCE OF UTERINE MUCOUS POLYPI. O HINTZE, *Zentralbl f Gynak* 52 2439, 1928

Examination was made of 225 polypi of the cervix and 57 of the body of the uterus. In seven cases of benign cervical polypi recurrences were observed. Benign cervical polypi and cervical cancer occur rarely at the same time. Still less frequent is the coincidence of malignant polypi with cancer (one case). The histologic changes present in highly epidermoid polypi may be mistaken for cancer, especially if squamous epithelial cells have advanced deeply into the glands and have replaced the cylindric lining. Serial sections are sometimes needed to trace the origin of these deeply seated squamous epithelial nests from the surface epithelium. A positive mucin stain in these nests gives evidence of their genesis. Moreover, the normal shape of the glands is well preserved. In doubtful cases, the immature character of the cells, their atypical forms, point to a malignant nature. Polypi were found in all age periods (22 to 72). The fifty-seven polypi of the body of the uterus represent 20 per cent of the total number seen in a three year period. There are two types of polypi, the myomatous and the mucous. The marked proliferation of glands, their closely packed arrangement, their irregular branching and the stratification of their epithelial lining are often suggestive of malignancy and should be considered as that, if seen in the endometrium, but have to be regarded as benign changes if restricted to the polypi, on account of the favorable clinical experiences in these cases. Seventeen cases of this type were seen in a twenty year period, and in none of them was malignancy observed later. These polypi were usually located at the fundus, only one being located in a tubal corner.

W C HUELPER

Medicolegal Pathology

SUDDEN DEATH FROM HEART DISEASE WHILE MOTORING. E R LE COUNT and GEO J RUKSTINAT, *J A M A* 92 1347, 1929

Three cases illustrating sudden death from coronary and myocardial disease while motoring are reported.

ACUTE PHOSPHORUS POISONING FROM ROACH PASTE STAFFORD McLEAN,
AILDRED MACDONALD and RUTH C SULLIVAN, J A M A 93 1789, 1929

Roach paste containing 1.19 per cent elementary phosphorus is dispensed in a container which is not labeled in a manner emphasizing the danger to children from its careless use

A portion of this paste was placed in easy access of a child, aged 18 months. Fatal phosphorus poisoning followed. This was proved chemically and by autopsy.

Chemically there was manifested liver injury as shown by a breakdown in carbohydrate, nitrogen, bile pigment, fibrin and cholesterol metabolism.

The autopsy observations indicating the harm due to phosphorus were chiefly manifested as hemorrhages in the pleura and pericardium and as lesions of the stomach, kidney, liver and striated muscle.

AUTHORS' SUMMARY

FATAL OCCLUSION OF LARYNX BY ASCARIS LUMBRICOIDES M B D DIXEY,
Edinburgh M J 36 111, 1929

Sudden death took place in a girl, aged 8½ years, from occlusion of the larynx by two large ascarid worms.

MEDICOLEGAL SIGNIFICANCE OF BLOOD GROUPS F SCHIFF, Lancet 2 921, 1929

Certain erroneous statements about the significance of the blood group in questions of paternity are discussed and corrected. More than 5,000 medicolegal examinations for blood groups have been made in Germany and the validity of the blood group test is now firmly established in this and other countries (Denmark, Sweden, Norway, Austria). Recently a committee composed of representatives of forensic medicine, serology and genetics, convened by the Reichsgesundheitsamt, expressed the opinion that the determination of the blood groups when done by an expert "is a reliable method which may be used advantageously for forensic purposes, especially for the exclusion of paternity." In about 5,500 cases, paternity was excluded in 8 per cent according to Schiff. In Germany an effort is made to safeguard officially the reliability of blood group tests.

INFANTICIDE BY THE MOTHER DURING BIRTH G SCHMIDT, Arch f Kriminol
83 260, 1928

There are records of a projecting arm or even the head being severed by the mother with sharp instruments before the child has completely passed out of the birth passage, also of infanticide by stabbing the presenting intravaginal portions of the infant. The child has also been strangled when only the head was born. This report by Schmidt is another of these rare intrapartum murders. The mother beat the child's head with her bare fists so that the top and right side of the cranium was extensively fractured, and the child died a few hours after birth. When the physician arrived, the feet were still in the vagina, and the bed was bloody where the child's head lay.

E R LE COUNT

AN EFFORT TO USE QUICKSILVER AS A POISON H KOCKEL Arch f Kriminol
83 308, 1928

It is not generally known that metallic mercury is relatively innocuous when swallowed. After shaking the feces of two bowel movements of an illegitimate child with a concentrated solution of potassium chloride, the feces floated and mercury noted by the mother-in-law sank to the bottom. Altogether 3,477 Gm., about 4¾ pounds avoirdupois weight, was recovered. The father had endeavored to poison the child. There were no symptoms of poisoning.

E R LE COUNT

DEATH AFTER TRIBROMETHANOL ANESTHESIA D KALLMANN, Deutsche med Wchnschr **55** 1221, 1929

A girl, aged 19, who was given 45 Gm of tribromethanol in 200 cc of water by rectum to induce surgical anesthesia, never regained consciousness and died of cardiac failure in seventeen and a half hours. At postmortem examination, there was found only an extensive superficial erosion of the lining of the large bowel, especially of the sigmoid colon. It was noted that the urinary bladder was empty although the patient had passed no urine since the anesthetic was administered. Histologically, there were marked fatty changes of the kidneys and liver.

PAUL J BRESLICH

THERMOMETER WOUND WITH MERCURY POISONING DRUGG, Deutsche med Wchnschr **55** 1637, 1929

A nurse, in shaking down the column of mercury in a thermometer, injured her left index finger with broken glass. The wound healed rapidly but a swelling of the finger developed, and the x-ray examination disclosed finely divided mercury in the tissues. Symptoms of mercury poisoning were noted soon after, and these gradually became more severe in spite of repeated efforts to remove the mercury surgically. At the end of seven months, the finger was amputated and the patient recovered.

PAUL J BRESLICH

CARCINOMA AND TRAUMA J SEIFFERT, Deutsche Ztschr f Clin **205** 145, 1927

Many factors are said to be concerned with the causation of new growths. In reviewing injuries during the World War, tumor as a consequence of injury was not found. The alleged more rapid growth of tumors already existent and directly injured has little real foundation, with the possible exception of the highly malignant tumors which develop from moles when they are injured or infected. The article is theoretical and chiefly a review of literature.

E R LE COUNT

DIMETHYLSULPHATE POISONING H STROTHMANN, Klin Wchnschr **8** 493, 1929

Two patients with mild, and one with severe, $\text{SO}_2 \begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{CH}_3 \end{smallmatrix}$ poisoning were observed clinically. The symptoms are similar to those in exposure to severely irritating fumes. Important lesions, therefore, are produced in the respiratory passages and the eyes. Only a few reports of $\text{SO}_2 \begin{smallmatrix} \text{CH}_3 \\ \diagup \\ \text{CH}_3 \end{smallmatrix}$ poisoning are recorded.

EDWIN F HIRSCH

IS THE INGESTION OF PULVERIZED GLASS HARMFUL? GREIFF, Munchen med Wchnschr **76** 1460, 1929

The feeding to rats and cats of pulverized glass mixed with various foods failed to cause digestive disturbances or anatomic changes of the gastro-intestinal tissues.

EDWIN F HIRSCH

ATOPHAN AND ICTERUS KETIL MOTZFELDT, Norsk Mag f Laegevidensk **90** 283, 1929

The different chinolin preparations (cinchophen, etc.) are now widely used in the treatment of rheumatic and arthritic pain. These preparations are recommended without restriction in textbooks on pharmacology as less toxic than the salicylates. A case of severe toxic jaundice is reported in a woman, aged 27, from phenyl-chinolin-carboxylic acid. The patient had taken 117 Gm in two periods during two months. A review of the literature reveals several similar cases during the past two years, and at least twenty-five cases are known in all, in ten of which death occurred from acute yellow atrophy of the liver.

Technical

ON THE USE OF A METHOD FOR THE ISOLATION OF ASCARIS EGGS FROM SOIL
L A SPINDLER, Am J Hyg **10** 157, 1929

The egg isolation technique was found to be of value in determining sources of infestations with *Ascaris* which were obscure due to the absence of soil pollution.

In areas in which soil pollution was occurring regularly the number of embryonated eggs in the sample was found to be much less than the number of one-celled and developing eggs. In one area, however, (Roaring Fork) where human stools were rarely found, embryonated eggs were much more numerous than one-celled and developing cells. This indicated that there had recently been a change in the soil pollution habits of the people in Roaring Fork.

It was found that the number of embryonated eggs in the isolations was surprisingly small, indicating that *Ascaris* eggs die much more rapidly in the soil than is commonly believed. This suggests that *Ascaris* eggs do not live over the winter in any number and that infestations in the spring are dependent on the development of a new crop of eggs and not on those living over from the previous fall.

AUTHOR'S SUMMARY

DEXTROSE IN SYNTHETIC MEDIA FOR THE TUBERCLE BACILLUS R R
HENLEY, Am Rev Tuberc **19** 660, 1929

Synthetic mediums containing dextrose afforded a more rapid growth of *Bacillus tuberculosis* than did the same mediums free from sugar. The results confirmed the recently reported observations of Frouin and Guillaume, since it was found that the growth of *B. tuberculosis* on synthetic mediums was influenced by the relative proportion as well as by the actual amount of the different constituents of the mediums. A medium is described which in six weeks afforded yields of bacteria weighing 2 Gm, dry weight, per hundred cubic centimeters of culture fluid.

H J CORFFR

OBSERVATIONS ON SOME OF THE FACTORS INVOLVED IN FILTRATION EXPERIMENTS FRANCIS B GRINNELL, J Bact **18** 175, 1929

Neither the rate of flow of distilled water nor the pressure required to bubble air through a filter under water is a safe guide as to whether or not the filter will hold back bacteria. An old culture of *B. prodigiosus* will pass through a filter which is impermeable to a young culture. The nature of the suspension fluid is of great importance in determining whether or not particles of a given size will pass through a filter. Victoria blue B will pass through Berkefeld filters, if dissolved in hormone broth. Young cultures of *B. prodigiosus* will pass through Berkefeld filters V and N, if suspended in a modified hormone broth or in alkaline extracts of certain animal or vegetable cells. The chemical composition of the substance present in hormone broth and in certain cell extracts which facilitates filtration through Berkefeld filters has not been determined.

AUTHOR'S SUMMARY

A NEW FIXATIVE FOR MITOCHONDRIA J GOUGH and J D FULTON, J Path & Bact **32** 765, 1929

Mercuric acetate may be used as a fixative for mitochondria after simple formaldehyde fixation. The chemical action is the formation of addition compounds with unsaturated centers. The intense staining with acid fuchsin after this fixation is accounted for by the capacity of mercuric acetate to form an insoluble purple compound.

AUTHORS' SUMMARY

SPUTUM EXAMINATIONS IN TUBERCULOUS PATIENTS E BAJZA, Beitr z Klin d Tuberk **72** 202, 1929

So-called concentration of the sputum with antiformin for the bacterioscopic demonstration of tubercle bacilli is useless. In 99 per cent of all bacilli-carrying sputums, elastic fibers were demonstrated.

MAX PINNER

A SIMPLE METHOD FOR BILATERAL THORACOGRAPHY ANTHONY and HANSEN, Beitr z Klin d Tuberk **72** 217, 1929

A simple apparatus is described by which the excursions of any point of the chest wall can be accurately recorded.

MAX PINNER

RAPID HISTOLOGIC DIAGNOSIS OF MALIGNANT TUMORS R DENGLE, Zentralbl f Gynäk **53** 457 1929

A rice seed size piece of tissue removed from the suspected part is dissected with the help of two needles in 0.9 per cent NaCl solution. It is examined with high magnification and almost closed diaphragm after the addition of a drop of 1 per cent acetic acid. The nuclei of the tumor cells are counted according to their size. The smallest nuclei present are counted with 1, the nuclei twice the size with 2, etc., to 7. The result is expressed as a quotient of the number of different sizes counted divided by the total number of nuclei counted. If fifty nuclei are counted, the quotient for carcinomas is always above 0.1, usually 0.14. The range, in general, is from 0.06 to 0.14 (from 3/50 to 7/50). The diagnoses were made from fresh tissue in 100 cases and later substantiated from sections prepared with the usual methods.

W C HUEPER

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Nov 14 1929

J HAROLD AUSTIN, Presiding

THE OCCURRENCE AND SPREAD OF TUBERCULOUS INFECTION EUGENE L OPIC

I shall present a conception of tuberculosis by no means new which explains many obscure aspects of its pathogenesis and promises to modify profoundly procedure for its control. Briefly stated it is that tuberculosis of early life has the characters of a first infection, whereas tuberculosis of later life is a disease modified by acquired immunity.

Tuberculosis in infancy and early childhood resembles that produced experimentally in susceptible animals. Pulmonary tuberculosis in adults has, however, little resemblance to tuberculosis produced by the usual inoculation of animals. In sharp contrast with the tuberculosis of early childhood it long remains localized in the parenchyma of the lung and even though a whole lobe is implicated the lymph nodes at its hilus exhibit none of the characteristic changes of tuberculosis.

Roentgenologic films prepared from lungs removed after death are an effective aid in the discovery of the calcified scars of healed tuberculosis acquired during childhood. By this means one seldom fails to obtain proof that those who die from the chronic pulmonary tuberculosis usual in adults have sustained an earlier infection.

Human pathology furnishes a significant illustration of the danger accompanying protective inoculation. The early tuberculous infections of childhood afford a certain degree of protection against reinfection and when it occurs profoundly modify its course, yet these childhood infections vary widely in intensity and even when long concealed or latent may ultimately cause active disease and death.

Changes that occur at the site of reinfection with tubercle bacilli resemble closely those that occur in animals sensitized to foreign protein. When foreign protein is first injected into the skin of a normal animal it rapidly leaves the site of injection and enters the circulating blood. In the animal that has been immunized (and sensitized) reinfection with the foreign protein produces an intense inflammatory reaction with necrosis at the site of entry, the foreign protein is arrested by the inflammatory reaction at the site of injection, and fails to enter the circulating blood. Krause and Willis have recently demonstrated by inoculation of excised tissue into guinea-pigs that there is in normal guinea-pigs rapid dissemination of tubercle bacilli from the site of inoculation, whereas in animals previously infected dissemination is retarded.

Experimental transmission by contact rather than by inoculation is a method of study that has not received the attention it deserves. Systematic studies of the experimental epidemiology of tuberculosis have been made by Perla and by Lurie at the Henry Phipps Institute. A large part of those who are engaged in the experimental study of tuberculosis believe that spontaneous tuberculosis of guinea-pigs occurs seldom if at all. When normal guinea-pigs were kept in cages with others that were infected, from 22 to 60 per cent acquired tuberculosis after about seven months, the number varying with crowding and other conditions.

At the present time the epidemiology of human tuberculosis can be studied more satisfactorily than that of animals.

Until the last few years little has been known concerning the distribution and severity of tuberculous infection among those who give no evidence of the disease and are presumably in good health. It is evident that no accurate knowledge

of the epidemiology of tuberculosis is obtainable as long as these latent infections are ignored. During the last six years, the dispensary of the Henry Phipps Institute has been organized to assemble by its routine operation information concerning the occurrence of latent as well as clinically manifest tuberculosis, to trace the spread of infection by contagion within the household and elsewhere and finally to determine by observations continued over a period of years under what conditions latent develops into manifest disease.

A study of the spread of tuberculosis in families has been undertaken by Dr McPhedran and me. This study has demonstrated how frequently advanced latent lesions develop into manifest disease. The recognition of advanced latent tuberculosis furnishes a means by which the onset of tuberculosis may be predicted within certain limits years even before it has begun to undermine health. Roentgenologic studies have revealed the frequency with which apical lesions occur in adolescent children of families exposed to open tuberculosis. In families in which husband or wife suffered with open tuberculosis we found evidence that the infection had been transferred to the consort in nearly half of those who were examined.

A survey of tuberculosis among children in the public schools of Philadelphia made by Dr Hetherington, Dr McPhedran, Dr Landis and me during the last three years has revealed the frequency with which infection varying in character and extent occurs in children who are presumably healthy. This survey has shown that 0.5 per cent of the school children we examined have manifest tuberculosis recognizable by physical examination and roentgenologic films. Latent tuberculous infiltration of the lungs of the type of childhood was found in 2 per cent of children and was evidently more significant in younger children. Latent apical tuberculosis (adult type) was found in 1 per cent of children, in large part in high-school pupils between the ages of 15 and 18 years. Of boys of high-school age, only 0.4 per cent had clinically recognizable tuberculosis, whereas of girls 1 per cent was affected. Manifest tuberculosis was found in 0.6 per cent of white children between 12 and 18 years of age and in 2.4 per cent of colored children of the same ages.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Nov 21, 1929

HARRISON S. MARTLAND, *President*

POSTMORTEM BLOOD CHEMISTRY IN RENAL DISEASES SILIK H. POLAYES and EDITH HERSHEY (by invitation)

Chemical analyses, including that of the creatinine and urea content were made post mortem on the blood of 100 patients with various diseases. Only those cases were chosen in which previous chemical analyses were made during life, so that comparisons could be made between antemortem and postmortem determinations. It was found that the postmortem figures for urea were highest in those cases which showed high postmortem creatinine values, namely, in the cases of renal disease with average antemortem creatinine values of 5.6 mg per hundred cubic centimeters of blood. The figures for urea, however, were found to be unreliable as an index of the antemortem renal status. The creatinine values post mortem, on the other hand, were found to be helpful in determining the status of the renal function during life. Whenever the postmortem figures for creatinine were 4 mg or more per hundred cubic centimeters of blood, the values obtained during life were over 3 mg per hundred cubic centimeters of blood, and there were other evidences of severe renal disease clinically as well as anatomically.

1 Postmortem determinations of blood creatinine and urea are often helpful as an aid in obtaining the status of the renal function during life.

2 The values for urea are not as helpful as those for creatinine

3 A creatinine content of 4 or more mg per hundred cubic centimeters of blood post mortem indicates marked retention of creatinine during life and therefore severe renal insufficiency

CHANGES IN THE INTRAHEPATIC BILE DUCTS FOLLOWING CHOLECYSTECTOMY
AN EXPERIMENTAL STUDY JOHN E. SUTTON, JR (by invitation)

For a number of years, certain changes in the biliary system have been known to occur following cholecystectomy. In 1917, Judd and Mann reported the dilatation of all of the extrahepatic ducts after the removal of the gallbladder, and they showed that this is due to the action of the sphincter of Oddi. Sweet has observed a marked rise in the blood cholesterol following cholecystectomy. Normal values were not found for forty days or more after the operation. The development of jaundice after obstruction of the common duct is distinctly influenced by the loss of the gallbladder. In normal dogs, according to Mann and Bollman, bilirubinemia develops in from twenty-four to thirty-six hours following ligation of the common duct, whereas after cholecystectomy bilirubinemia develops in from three to eight hours after biliary obstruction. The parietal sacculi, which are normally found as small pouches extending from the lumen into the fibrous walls, enlarge to an appreciable degree following cholecystectomy, and it has been suggested that this enlargement compensates in a way for the loss of the gallbladder. In animals which do not possess gallbladders there is evidence of a mechanism capable of performing some functions of a gallbladder. In the horse there is an elaborate development of the parietal sacculi, according to Sweet, in the rat, as shown by Higgins, there is an extensive system of blind tubules in connection with the intrahepatic bile ducts, which twine about the branches of the portal vein. Furthermore, the liver bile of the rat, as estimated by McMaster, contains eight times as much pigment as the liver bile of the mouse, which possesses a gallbladder.

In this study, simple cholecystectomy was performed in eighteen dogs which were allowed to survive for varying periods of time up to seventy-seven days. The animals were killed with ether, the livers were removed intact and a 12 per cent solution of silver gelatin was injected through the common duct, under a pressure of from 100 to 180 mm of mercury, until the biliary system was completely filled. Under a constant pressure the specimens were placed in an ice-cold 5 per cent solution of formaldehyde which hardened the gelatin and fixed the tissue. Six normal dogs' livers were treated in the same manner and used as controls. Microscopic sections of the gallbladder and the intrahepatic bile ducts of the normal dogs, and sections of the intrahepatic ducts of the dogs 15, 22, 40 and 77 days following cholecystectomy were studied. The original intent was to study the changes which occur in the parietal sacculi following the removal of the gallbladder, but a study of the sections revealed changes of far greater importance.

Without exception, all sections from the controls show that there was a normal cuboidal epithelium in the intrahepatic ducts, and that the mucosa of the gallbladder was covered with high columnar cells normally arranged on folds projecting into the lumen. The duct epithelium following cholecystectomy showed definite changes in all specimens. Fifteen days after operation the surface of the epithelium was irregular, new cells projected into the lumen of the ducts, and there was apparent bud formation. These projecting cells contained light staining, large, irregular nuclei and their margins were not clearly defined. In many areas the cells were present in multiple layers. Forty days after cholecystectomy, well defined alterations of the duct epithelium were seen. Numerous mucous folds and villi of varying size were seen projecting into the lumen of the ducts, and the epithelial cells were elongated and roughly oval, the cells approached the morphologic appearance of the epithelial cells of the gallbladder. The appearance of the duct epithelium seventy-seven days after cholecystectomy fulfilled the promise of the earlier changes. The mucous folds were longer and

the epithelial cells were high columnar with oval or ellipsoid nuclei, the long axes of which were perpendicular to the bases of the cells. The microscopic picture of the tip of one of these mucous folds was identical with that of the tip of a mucous fold in the normal gallbladder.

The only operative procedure used in this investigation was simple cholecystectomy, which was done on eighteen dogs, no injections of any material were made into the bile ducts while the dogs were alive. The injection of the gelatin solution after death served to distend the ducts and to prevent distortion of the walls of the duct during the fixation in formaldehyde. Therefore all projections found in the lumina of the ducts were true mucous folds and were not due to infolding of the walls of the duct.

In the normal dog, removal of the gallbladder is followed by prompt changes in the intrahepatic bile duct epithelium. In this study these changes have been followed in sequence. The development of mucous folds in the ducts, increasing the epithelial surface to a marked degree, and the change of the epithelial cells from the cuboidal type, with no real resemblance to the gallbladder cells, to high columnar cells having morphologic characteristics identical with those of the normal gallbladder lead to one conclusion. Removal of the gallbladder is followed by compensatory changes in the intrahepatic bile duct epithelium, these changes must mean that the bile duct epithelium can adapt itself to perform functions of the gallbladder.

From the examination of a number of specimens of human livers (by permission of Dr. Krumbhaar, McManes Laboratory of Pathology, University of Pennsylvania) it appears that these changes also occur in human beings after cholecystectomy and in the presence of chronic cholecystitis and cholelithiasis.

SOME OBSERVATIONS ON BLOOD GROUPING ARTHUR M. TIBER (by invitation)

Ten thousand specimens of blood were examined for grouping by the open macroscopic method of Vincent, 46.5 per cent fell into group O, 36.4 per cent into group A, 13.5 per cent into group B and 4.5 per cent into group AB. The material used for testing these specimens consisted of pooled specimens of group A and B serums. The grouping of the red cells was without fault in 9,985 specimens of blood. Fifteen showed questionable agglutination because they were either clotted or very anemic. The serum of a small number of persons was tested with known red cells and it was found that in nine cases the typing did not check with the results obtained by typing the red cells. In five cases, in which the donor and the recipient were of the same group, there was agglutination when the bloods were cross-matched. In 1,467 transfusions of blood there were but 2 deaths, one as a result of an error in technique and the other as a result of the use of a so-called universal donor, 10,242 cases of blood transfusion were collected from the literature, with 22 deaths from all causes in this series. 13 due to wrong types, 1 to primary disease, 4 to heart failure and 4 to unknown cause.

The following conclusions were given. The open macroscopic method of Vincent is efficient for determining the blood group of recipients and donors. Serum for testing should consist of pooled specimens of group A and B serums. Grouping by this method should be determined by testing the red cells alone. The classification of bloods into four groups is sufficient for the purpose of transfusion. The death rate for transfusions of blood is 0.39 per thousand.

DISCUSSION

PERRY MANHEIMS. About five years ago, at the Lenox Hill Hospital, a patient who was receiving a transfusion of 100 cc. of blood, showed symptoms of a typical transfusion reaction of incompatibility. The transfusion was stopped, and although the reaction was severe, the patient recovered. That was one case in which we did not do a cross-test because it was an emergency and we were hurried by the attending physicians. Since that time no transfusion, no matter how urgent,

has been done without a cross-grouping. We have not had any mortality. I believe that every case should be grouped and cross-tested, in addition to the grouping.

PHILIP LEVINE (by invitation) I should like to make a comment concerning the significance of the irregular reactions in general. Dr Landsteiner and I have examined numerous serums by the use of a sensitive technic and we have found that about 3 per cent of serums showed distinct atypical reactions at 20 C. At 37 C most of the reactions disappeared. About ten serums were observed which showed a distinct type of specificity.

The agglutinable property indicated by this agglutinin is influenced by heredity. A difference in its distribution in colored and white persons is also shown.

Another distinct type is a so-called subgroup division in group A. We found two atypical agglutinins α^1 and α^2 in some serums of groups A and AB. Group O cells, which are supposed to be characterized by lack of agglutinogens, react with agglutinin α^2 .

In agreement with Dr Tiber's paper we believe that there is not sufficient evidence at present that transfusion in cases with typical reactions is harmful.

REUBEN OTTENBERG I do not entirely agree with Dr Tiber for this reason. I think the minor differences that are pointed out by Guthrie and Houch probably do not lead to fatal results, but they can readily lead to errors in grouping. That is to say, there are certain persons belonging to group B whose serum will fail to agglutinate that of persons in group A, knowing that the person's cells have been grouped as group B, if one simply uses that serum as a group serum, and depends on it alone, one can readily make a mistake. The fact is well recognized. In a study of blood groupings, Guthrie and Houch were the first to emphasize that this particular subdivision occurred. If a person in group B has only serum agglutinin α and a person in group A only red cell agglutinogen α^2 , one serum will fail to agglutinate the other. Only this week an intern was puzzled by such a case. A person with different sets of typing serums was put down as type B, and then as a type AB. On going over the problem with him more carefully and testing the serum of the subject we found that there was a type B in the test serums which failed to agglutinate certain serums of group A. For that reason I feel that if one knows all about the subject, is aware of these occasional happenings, and always uses two or three serums of each type to do one grouping, then it is safe to go ahead and rely only on grouping. But if one works in a routine way one may now and then have a serious accident in the grouping itself. For that reason I think one should always, except in emergency, do cross-tests as well as grouping.

With regard to extra-agglutinins, two or three years ago I published a case in which death from hemolysis followed blood transfusions in which an irregular agglutinin was demonstrated. I do not know whether this is extra-agglutinin I of Levine or another of the irregular agglutinins. We have not been able to identify it because the donor, who was a professional donor, would not come back for further investigation. Death was undoubtedly caused by hemolysis, the recipient and the donor both belonged to group B, except for the extra-agglutinin that agglutinates and hemolyzes the cells of certain other persons in all four groups.

JACOB WERNE (by invitation) A practically important and frequently neglected factor in performing the matching is that of time. I wonder whether any of the anomalous observations reported in Dr Tiber's series may not have been made because insufficient time was allowed for agglutination to occur. Several times in doing the routine cross-match, I have had the unpleasant experience of reporting compatibility after waiting the conventional twenty minutes, only to notice by chance some fifteen minutes later the occurrence of definite agglutination. Dr Scannell once suggested to me that placing the preparation in the icebox would accelerate agglutination, if this were going to occur. I have found this measure of considerable help.

SILIK H POLAYFS We ought to be a little more careful in distinguishing the reactions due to anaphylaxis from those due to interagglutination. At the Jewish Hospital in Brooklyn, we recently had a case in which the anaphylactic reaction following a transfusion so closely simulated an interagglutination reaction that it was difficult to differentiate it clinically. We sent the blood to the Rockefeller Institute. Dr Levine analyzed it and found nothing irregular about it. Both the donor and the patient were of group A. We are now certain that it was an anaphylactic phenomenon. In a subsequent transfusion in the same case, the reaction was definitely controlled by the injection of epinephrine. I feel certain that a good many of these reactions reported as interagglutination reactions are really not such, but are simply anaphylactic reactions.

ARTHUR M TIBER One of the speakers suggested placing the reaction slides in the icebox. It is well known that cold agglutinins act at icebox temperature 0 C. More confusion would be found if the slides were placed in the icebox than if they were kept at room temperature. If he had said at 36 C, I would be more apt to agree with him because many of the irregular reactions can be ruled out at that temperature.

We use the open macroscopic method of Vincent and watch the reaction for from five to ten minutes only. Any one who has used this method knows that after thirty minutes' observation he has a clot on his slide, with nothing to read.

As to Dr Ottenberg's statement, I think it is true that the serum of certain patients is weak in iso-agglutinins, and if one uses serum from but two persons for testing purposes the results may be fallacious. At Bellevue we have avoided these errors by pooling the serums of the same type. In this way, if an anomalous serum is included, it is diluted by the other normal serums, and instead of lacking an iso-agglutinin, we have the normal titer of iso-agglutinin.

Dr Levine's statement about the subgroups is an important one, particularly in forensic medicine. As to the necessity of determining the presence or absence of these subgroups, I think it is unimportant, so far as blood transfusion is concerned, especially when one considers that there were but four deaths directly attributable to the transfusion in the 10,242 cases cited. This gives a death rate of 0.39 per thousand transfusions. I know of no other procedure in medicine or surgery in which the death rate is as low, and I believe it proves that our present procedure of choosing blood donors is the method of choice.

A METHOD FOR THE STUDY OF BONE MARROW CYTOLOGY ABRAHAM S GORDON (by invitation)

The purpose of this work was to study the elements of the bone marrow from a number of angles such as the determination of the quantities of the different types of cells per unit volume of bone marrow, the relative proportions of the various types of elements to one another, and the character of the different types of cells in their various stages of differentiation, hoping possibly to follow these stages to their origin in the form of the primordial cell or cells.

In the quantitative estimation of the cellular content of the bone marrow, the principle used was the same as that for counting the cells in the circulation: an acetic acid solution for the nucleated elements, and a citrate solution for the red cells as well as for all elements. The method may be termed "the dilution method." In all cases only rib marrow was used for the quantitative estimation. In most cases a 1:9 dilution of the marrow was used, which gave a suitable solution for counting and a convenient factor for calculation. Some cases required a modification of this proportion.

Special 3 by $\frac{3}{8}$ inch (7.62 by 0.95 cm) graduated tubes were used. One of these contained 0.9 cc of the acetic acid solution, and another 0.9 cc of the citrate solution. To each of these tubes 0.1 cc of rib marrow was added, and the tubes were shaken for about fifteen minutes. The solutions were then drawn up into the proper blood-counting pipet to the 0.5 or 1 mark, as the case required, and the rest of the pipet filled with the appropriate solutions. The pipets were

again shaken for about ten minutes, and the counts made in the Neubauer hemocytometer. The calculations were made accordingly.

In all cases the total number of all cells and the total number of nucleated cells were counted separately from the different pipets in different counting chambers. Then the total number of red cells and the total number of nucleated cells were counted separately in the same chamber, and the two independent figures for the nucleated cells from the two different solutions were compared. In no case were the final figures recorded unless the separate figures corresponded, allowance having been made for the average technical error. All nucleated cells were counted in one group, comprising all myeloid cells, all nucleated red cells, including normoblasts, megaloblasts, and still earlier forms of the erythroid series, and all lymphoid cells, as well as endothelial cells and all forms of unclassified cells. In some cases, when indicated, the megakaryocytes were counted separately. The further subdivision of these cells becomes a problem for differential study, for attempts were not made to differentiate the various types of cells in the counting chamber.

In the differential study, blood serum was used for dilution. Autogenous serum, of course, would have been ideal, but as this was not always procurable, the blood group of the person was determined from the marrow, and the corresponding serum was used for dilution. The proportion of serum to marrow cannot be fixed for use in all cases as each marrow requires an amount commensurable with its own physical characteristics, and the proper quantity to be used must be judged from experience. Sometimes several mixtures must be made before a proportion is obtained that gives the proper smears. The Romanowsky dyes were used for staining. In some cases, such as myeloblastic leukemia, lymphatic leukemia, agranulocytic angina, aplastic anemia or any other form of severe anemia of unknown etiology, the results were counter-checked with the supravital stain and the oxydase stain, but these were not used for control in all cases.

DISCUSSION

MAX LEDERER The method was developed originally from the way in which our routine bone marrow studies are made. The entire rib is removed and grasped between two pairs of strong forceps especially made for that purpose, and the contents are squeezed into Helley's fluid. It is surprising how much marrow can be obtained from a rib, except in elderly people in whom the ribs are fragile. However, if care is taken, the rib does not fracture. The marrow flows easily and can be sucked into a pipet. The idea occurred to Dr. Gordon of using isoserum for a person of the same blood group to which the patient belonged in making smears. At first he used a serum from groups A, B, AB and O respectively, but he learned later that serum from group AB could be used, since it contained no agglutinins. This serum can be kept in stock. The slide preparations show the detail of various cells to a fine degree. The method has not been presented for the purpose of pointing out diagnostic differentiations pathologically at this time, but rather to stimulate studies and collect information from which practical conclusions can be drawn. This is important in view of the fact that studies of bone marrow in the living subject are being adopted as a diagnostic procedure, and it is essential that concentration of the individual bone marrow cell be studied, by the method described or a similar one. Postmortem material lends itself to this work very well. Up to the present time, a series of 100 cases has been studied, but far more material must be collected before any definite conclusions can be arrived at. The two methods are presented for further clinical study. If they are of any benefit, well and good, if not, they will be discarded, they must stand or fall on their own merits.

LOUIS GROSS I should like to ask Dr. Gordon whether he experienced any technical difficulty in sucking up bone marrow into a pipet, particularly fatty bone marrow. I should also like to know whether he made a series of counts on sections from different parts of the rib. I presume he did. If so, was any appreciable variation found in these counts?

ABRAHAM S GORDON Sometimes it takes hours of working with a specimen before a suspension is obtained that will give a uniform smear. Some marrows are easier to work with than others. Children's marrows are, as a rule, much easier than adults. The principal thing is to mix the marrow with a definite amount of serum. The exact amount depends on the type of marrow. Some marrows have much fat in them. After thorough mixing, the fat will rise to the surface. This will answer Dr. Gross's question of the difficulty of sucking up the solution from fatty marrow. We have no difficulty there because the fat rises to the surface of the solution, so that it can be removed easily. The removal of the fat does not interfere with the counting process nor with the final results, because we are starting with a definite volume, and the cellular content of the original volume is still present. We take the entire marrow, with the fat and blood.

As to counts from different parts of the rib, we have taken marrow from every part of the rib, from each end and from the center, and sometimes from different ribs of the same patient, and have found no appreciable difference in the results. When the marrow is squeezed out of the rib a certain amount is allowed to run out, thus an average of the marrow in the rib is obtained. If any destruction is taking place, especially of the red cells, it cannot be helped, nor can it be avoided.

Interesting observations were made, and some of the results were uniform. If there is an acute infection before death, the marrow will present a definite picture. If there is no acute infection and the patient dies from some chronic disease or infection the marrow will present another type of picture, and the cell content of the marrow will be almost constant. I do not know how constant it will be for different types of disease, age and sex. In the study that Lossen made of infants and children, there was also a great variation in the numbers, ranging from 200,000 or 300,000 to over a million. He was dealing with a more constant type of marrow, namely, acute infectious diseases in children, conditions in which the count should be higher and more uniform. Generally, we get a good idea of the bone marrow contents, both from the differential study and from the total number of cells.

MARKED DILATATION OF THE LEFT AURICLE OF THE HEART EDWARD A. BURKHARDT, JR (by invitation)

An Italian aged 23, presented symptoms of acute cardiac decompensation. The patient was found in a stuporous, semimoribund state, with extreme dyspnea and cyanosis. Physical examination showed a margin of cardiac dullness extending 50, 50 and 85 cm to the right of the midsternal line in the second, third and fourth intercostal spaces respectively. The apex beat was 132 and the radial pulse 112 per minute. Marked presystolic and systolic murmurs were present over the precordia. The patient died thirty-two hours after observation. Autopsy showed that the heart weighed 540 Gm. The left auricle was dilated to the right of the right auricle for a distance of 80 cm to the right of the midclavicular line at the fourth rib. Dilatation to the left was limited by the arch of the aorta. The left auricle had a capacity of 593 cc of fluid (after fixation). The auricle contained a thin mural thrombus and the mitral valve was stenosed to a slitlike opening, 2.2 cm in length. Increased intra-auricular pressure through an incompetent mitral valve plus a damaged auricular myocardium probably account for the marked left auricular dilatation.

LYMPHOSARCOMA WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM CHARLES DAVISON and JOSEPH J. MICHAELS, Detroit (by invitation)

The brain and the spinal cord are rarely the seat of direct invasion by lymphosarcomatous masses. Occasionally the structures about the central nervous system, such as the bones of the skull or the vertebrae, may show the presence of lymphosarcomatous nodules. The scarcity of cases showing secondary involvement of

the nervous structure, especially the report of only one case in the literature in which the spinal cord was compressed, is the reason for this presentation

Since 1922, twenty-six patients with lymphosarcoma were admitted to the Montefiore Hospital. Of these, seven cases presented neurologic signs, four of

Cases of Lymphosarcoma with Involvement of the Nervous System

No	Sex* and Age	Duration of Illness	Onset		Clinical Diagnosis	Neurologic Diagnosis	Response to Deep Roentgen or Radium Treatment	Results of Autopsy or Biopsy
			General Symptoms	Neurologic Signs				
1	♀ 61	1 year, 9 months	Gradual	Gradual	Lymphosarcoma	Strainedillary neoplasm	Improvement early without any response later (deep roentgen ray only)	Generalized lymphosarcomatosis, with metastasis to dura
2	♂ 40	1½ years	Sudden	Sudden	Lymphosarcoma, hydrothorax	Herpes zoster	Relief early, no response later (deep roentgen ray only)	Generalized lymphosarcoma, pleural effusion (extramedullary neoplasm)
3	♂ 32	9 months	Sudden	Sudden	Neoplasm of the right lung	Metastasis to cord possibility of subacute degeneration	Early improvement, no response later	Lymphosarcoma of right lung, empyema, extramedullary deposits
4	♂ 40	1 year, 11 months	Sudden	Sudden	Generalized lymphosarcoma	Generalized lymphosarcoma with involvement of the meninges at the base of the skull	Temporary remission of glandular enlargement early pain was not relieved	Generalized lymphosarcomatosis, with invasion of the middle and posterior fossae
5	♂ 64	Discharged in 1922 and not heard from since	Sudden	Sudden	Lymphosarcoma	Lymphosarcoma with invasion of the posterior cranial fossa	Early improvement, with recession of enlargement and symptoms	Biopsy lymphosarcoma
6	♂ 37	7 months	Sudden	Gradual	Lymphosarcoma of the left lung with metastasis	Lymphosarcoma with metastasis to the vertebral column	Improvement early, with no response later (roentgen ray and radium)	Pleural exudate containing tumor cells
7	♀ 38	8 months	Sudden	Sudden	Lymphosarcoma of the neck	Left peripheral facial palsy	No benefit from either roentgen ray or radium	Biopsy lymphosarcoma

* In this column, ♂ indicates male, ♀, female

which were verified postmortem. Three of the cases presented signs of compression of the spinal cord, the remaining one showing involvement of the brain.

Of the seven cases showing neurologic signs, two showed invasion (cases 4 and 5) of the cranial cavity localized chiefly in the middle and posterior fossae, four showed involvement of the vertebral column or the spinal meninges causing compression of the spinal cord or on the posterior roots resulting in herpes zoster (as in case 2), and one case involved the facial nerve peripherally (case 7).

Cases 4, 5 and 7 showed early involvement of the cervical lymph nodes, in two instances (cases 4 and 5) there was invasion of the cranial cavity. In the other cases the invasion of the glands of the neck did not occur until late in the disease.

In case 4, in which the cranial cavity was invaded, the brain tissue itself did not show any evidences of invasion by the lymphosarcoma, as usually seen in metastasis from other tumors, especially metastatic carcinomas. The invasion in this case took place by way of the lymphatics. As the brain proper is not supplied by lymphatics this readily explains the absence of invasion of the brain tissue by lymphosarcomas. The cases showing involvement of the spinal cord in the form of compression did not show enlarged cervical lymph glands until late in the disease. In none of these cases was the spinal cord directly involved.

Except for case 7, all of the seven cases in which deep roentgen and radium treatment was given showed a recession of the lymphosarcomatous masses, with improvement in the symptoms only early in the treatment. After a few treatments the enlargements and symptoms recurred and finally failed to respond. This is characteristic of all the lymphosarcomas.

The following conclusions were given. Twenty-six cases of lymphosarcomas observed in the Montefiore Hospital since 1922 were investigated, seven of which presented neurologic signs and symptoms.

2 In none of the cases was there a direct invasion of the brain or the spinal cord. The symptoms were due chiefly to compression from invasion of the skull, vertebrae or meninges.

3 Invasion of the cranial cavity took place only when the cervical lymph nodes were involved, and as observed in our series, when they were involved early.

4 Deep roentgen and radium treatment, while not a cure for the disease, gives some relief from the symptoms during the first few applications. The relief is chiefly due to the recession of the tumor which causes compression on the respective organs. When these enlargements fail to respond to treatment, improvement in the symptoms may not be expected. These cases, however, for a period of time are benefited a great deal by deep roentgen rays or radium. At present these are the best forms of palliative treatment.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Dec 9, 1929

HENRY C. SWEANY, *President, in the Chair*

EXPERIMENTAL FAT NECROSIS AND ISOLATION OF A CAUSATIVE FACTOR M. PINSON NEAL and MAX M. ELLIS

A lipase fraction has been isolated from fresh hog's pancreas, dried pancreatin (Armour's lot no 205257) and the dried seeds of *Arachis*, the peanut, and *Helianthus*, the common sunflower. The lipase fractions from each of these sources when injected intraperitoneally into white rats produced definite fat necrosis.

These lipase fractions were not thermostable, and were rendered inactive, so far as the production of fat necrosis was concerned, by treatment with ethyl alcohol in strengths above 50 per cent, they were water-soluble and were not injured by the presence of ether, toluene or xylene, they were not adsorbed by blood or animal charcoal, from either acid or alkaline solutions, they were extracted from both acid and alkaline material, and they did not digest fibrin, but were active in the splitting of ethyl butyrate.

The results obtained by injections of these extracts which had no effect on fibrin permit the conclusion that trypsin is not required in the production of experimental fat necrosis.

Histologic lesions of fat necrosis found six hours following injections of the lipase fraction derived from *Atachis*, in morphology and in staining reaction, showed damages to cell walls, cytoplasm, nuclei and cell fat content. Loss of nuclear material within six hours after injections showed, so far as the cell was concerned, the critical character of the process. The loss of nuclear material appears to be entirely by lysis. The earliest anatomic lesions were found sixteen and one-half hours after injections of the lipase fraction from hog's pancreas. Gross and microscopic lesions eight days after injections of *Atachis* material showed definite reparative reactions. The local limitation of the lesions of fat necrosis can be partially accounted for by the cellular wall, or zone of demarcation.

This experimental fat necrosis produced no definite clinical manifestations in the animals into which injections were made.

The assumption of Langerhans that lipase is an etiologic factor of fat necrosis has been proved experimentally by the use of lipase fractions derived from animal and vegetable materials.

DISCUSSION

H. G. WEISS. I wish to congratulate the authors on the splendid piece of work they have presented. I am, of course, particularly interested because for several years more than a quarter of a century ago I tried to find out what it was that caused typical fat necrosis, and, with the means at that time available, I was unable to separate a lipase from trypsin and still produce fat necrosis with a lipase. Blood and extracts from liver which are actively lipolytic would not produce fat necrosis. I thought that this might depend on the fact that there are several sorts of lipases, some of which hydrolyze one sort of ester and not another. I noted that Dr. Ellis spoke only of testing his lipases with ethyl butyrate. Did he determine whether they would hydrolyze triglycerides? Of course, in order to produce fat necrosis the lipase would have to hydrolyze triolein and tripalmitin. In the experiment in which the lipase was inactivated by alcohol, was there found to be close parallelism between the loss of ability to produce fat necrosis and the loss of fat-splitting activity? Of course, the crucial experiment here was the production of fat necrosis with artificial lipases prepared by Falk's method. Here certainly the presence of trypsin, either active or inhibited, can be excluded. In Dr. Neal's presentation no mention was made of the lesions produced by these artificial lipases, and I should like to know more about the effects they produced. Were areas of fat necrosis found in the thoracic cavity in these experiments? I have often seen them in fat necrosis produced by intraperitoneal injection of large doses of active pancreatic extracts.

M. M. ELLIS. The lipase fractions did hydrolyze triglycerides. In the alcohol treated extracts there was a parallelism between the loss of the fat-splitting ability and the property to produce fat necrosis, as the fat-splitting activity declined, so did the fat necrosis producing property. Experiments using the artificially prepared lipase fraction (following Falk's method) are in progress, and while the observations are suggestive, we are not prepared to give a final statement. Regions of fat necrosis were not found in the thoracic cavity of any of our 300 animals into which intraperitoneal injections were made.

M. P. NEAL. In the presentation of the pathologic phase of this work mention of the lesions produced by the artificial lipases was intentionally avoided because our observations to date are not considered conclusive.

SQUAMOUS CELL CARCINOMA OF THE TRACHEA PAUL J. BRESLICH

A white man, aged 60, complained of severe dyspnea of two days' duration. For six months he had had paroxysmal attacks of dyspnea occurring with increased frequency usually at night. There was also a persistent productive cough with hoarseness. There were no significant observations in the physical and roentgen examinations of the chest. Treatment failed to relieve the dyspnea and the patient lost strength rapidly. The postmortem examination disclosed a tumor in the

posterior wall of the trachea just above the bifurcation which narrowed the lumen to a slit a few millimeters wide. The tumor extended backward to the prevertebral fascia displacing the esophagus to the left. The surface of the tumor in the trachea was nodular and ulcerated, while the esophageal mucosa over the bulging mass was smooth and unchanged. Except for a small nodule in the lining of the esophagus just below the tumor and covered with smooth mucosa there were no metastases to other tissues. There was no evidence of an esophageal diverticulum or tracheo-esophageal fistula from which the tumor might have originated. The new growth seemed therefore to be primary in the lining of the trachea. The cells of the tumor were squamous epithelium, and in the literature are reported seven similar growths of the trachea.

(The complete report will be published in the *Journal of Cancer Research*.)

DISCUSSION

H. G. WELLS. In a case of carcinoma of the trachea with squamous cell structure, the exclusion of a primary carcinoma of the esophagus invading the trachea is difficult. I noticed that in the specimen passed around the esophagus is involved. I take it that the conclusion that this carcinoma arose in the trachea rather than in the esophagus rests on the lack of ulceration in the surface of the esophageal growth. Were there malignant changes in the deeper portions of the esophagus lining?

E. R. LECOUNT. Growths arising from esophageal diverticula need consideration.

E. F. HIRSCH. The conclusion that this tumor probably arose in the trachea or possibly contiguous tissues but not of the lining of the esophagus was reached because a bulky ulcerated tumor was found occluding the lumen of the trachea, because the two submucous nodules of the esophagus were much smaller, were covered by a smooth mucosa and had the appearance of small metastatic nodules, and because the stratified squamous epithelium of the esophagus covering the nodules examined in a number of places was regular and the deeper portions nowhere invaded the submucosa.

POLYPOID PERICARDITIS MILTON G. BOHROD

A white man, aged 27, died of cardiac decompensation following an old, partly calcified mitral and aortic endocarditis. Hanging into the pericardial sac from the point of reflection of the parietal pericardium from the right auricle posteriorly, there was a mass consisting of several dozen polyps, some of them solid, most of them filled with blood in various stages of inspissation and with various degrees of organization. The blood spaces were lined by a single layer of endothelium. The walls of the cysts contained macrophages filled with blood pigment.

The tissue between the polyps was loose and fibrillar, with many capillaries, and with many large pale cells resembling macrophages. The latter were often grouped into nodules about a blood vessel, thereby resembling Aschoff nodules. On the surface epicardium and on many of the polypi there were accumulations of fibrin and red blood cells.

This case seems to illustrate a peculiar mode of healing in a rheumatic pericarditis. No such polypoid mass has ever before been reported. The polypi are probably formed by the fusion of partly organized fibrin masses, the gaps between them having previously become lined by endothelium. Small endothelial lined spaces are common in a healing pericarditis, and occasionally small cysts are seen. Lanche has reported the presence of a few cysts the size of a pea in one case. The blood in the polyps seems to have come from a previous hemopericardium.

DISCUSSION

E. R. LECOUNT. The title is rather unfortunate in suggesting another variety of inflammation. Organizing pericarditis with multiple polypi might be better.

Book Reviews

DIE FRAGE NACH DEM URSPRUNG DER ENDOMETRIOIDEN HETEROTOPEN BEIM GESCHLECHTSREIFEN WEIBE. VON KONRAD HEIM, Privatdozent für Geburtshilfe und Gynäkologie, Oberarzt an der Klinik. Aus der Universitäts-Frauenklinik Leipzig. Berlin: S. Karger, 1929.

In this monograph Heim, of Leipzig, undertakes an analysis of all types of endometrial heterotopy in the sexually mature woman, using the term heterotopy in the broadest sense so as to include adenomyosis uteri externa as well as intra-uterina and differentiating sharply between blastomatoid adenomyoma and adenomyosis. He reviews the various theories of origin of these growths, including the mesonephros hypothesis and the fetal derivation, with a detailed description of the embryologic development of this area.

The postfetal theories are discussed at much length: the direct origin of adenomyosis uteri interna from endometrium (Cullen), the serosal epithelial theory of Iwanoff, Meyer, Lauche, and Fischel, the transplantation theory of Sampson and the Halbanian theory of metastatic hysterio-adenosis.

The author's own material consists of eighteen cases in women between the ages of 25 and 50, of adenomyosis rectovaginalis, adenomyosis uteri externa, adenomyosis externa des ligamentum rotundum, tubal adenomyosis and adenomyosis interna. Chocolate cysts of the ovaries were not always found. The main purpose of the monograph is obviously an attack on Sampson's implantation theory, and since Germany is the stronghold of its antagonists, all the Teutonic artillery is arrayed against it. Heim considers each of the arguments given by Sampson in support of the latter's explanation of many ectopic endometrioses. Sampson found the condition in about 20 per cent of all his gynecologic patients. Heim finds no parallel for this figure in German surgical statistics. In two large institutions in which he had personal opportunity to look over the records and in which from time to time a special outlook for these conditions was kept he was able to encounter only a modest amount of material as compared with what he calls the fanciful, imaginary American numbers (den phantostisch anmutenden Amerikanischen Zahlen)? The fact that endometrial heterotopy is encountered only during menstrual life he thinks can be utilized just as easily to support a serosal epithelial metaplasia by accepting special hormonal changes. "Uterine mucosa-like is by no means uterine mucosa." Robert Meyer's antipathy to expressions such as endometriosis, endometrioma, etc. is based upon such reserved judgment.

The author sees little support for the implantation hypothesis in the location of many growths about the tubal funnel. Also the idea that normal body cells can be pulled from their foundations simply by a needle prick or suture and be able to grow in a strange and new environment he regards as purely speculative. He admits, however, that most of the mechanical prerequisites for the implantation theory are adequately fulfilled.

The biologic suppositions involved in the acceptance of the viability and transplantability of menstrual desquamate are considered the crux of the Sampsonian idea. The investigations of Sekiba of Aschoff's institute and of Bohnen of Schroeder's clinic are reviewed and the author's own work on the strata of the desquamation is presented. Heim admits great variation between persons and also in the same person. In all the large tissue fragments studied as early as they loosened themselves (sic) he found histologic signs of necrobiosis. The shedding appeared to continue down to the basalis, which showed no changes. The lack of vitality of menstrual desquamate he believes proved beyond all doubt.

The experimental transplantation of endometrial tissue by Jacobsen, Albrecht, Katz and Szenes, Michon and others carries little weight with the author since the endometrial fragments used were not from menstrual desquamate. Heim attempted

in vitro culture of human uterine mucosa from menstrual and intermenstrual periods and obtained a lively growth of cells which apparently he was not able satisfactorily to classify. Cron and Gey are criticized as being too easily convinced of the epithelial nature of cells growing in their menstrual cultures.

The monkey, naturally, is regarded as the best of the lower animals for the experimental study of endometrial heterotopy. Heim used five monkeys, two of which died, leaving one mangabe and two rhesus for study. He (1) sowed the superficial layers of their decidua menstrualis in the peritoneal cavity, (2) established a fistula between the uterus and pelvic cavity during menstruation and (3) planted fresh human menstrual sequestrums on the peritoneum or on the ovarian serosa of the sexually mature female monkey and at the same time injected ovarian hormone. After forty-one, forty-eight and sixty-two days no endometrioidal growth was obtained in any of the three animals. It might be added in parenthesis that recently Fraser (*J Obst & Gynaec Brit Emp* 36 590, 1929) reported the first case of spontaneous endometriosis in a monkey, *Macacus rhesus*. Hence after considering his anatomic studies and transplantation attempts Heim concludes that fragmented menstrual tissue has no growing power and that Sampson's theory while theoretically admissible is of doubtful validity. He quotes Robert Meyer as stating with sorrow that Sampson should be so assuming in the choice of his proofs referring specifically to the latter's well illustrated article on embolic endometriosis which contained many unretouched photomicrographs of endometrial fragments in uterine venous sinuses (*Am J Path* 3 93, 1927). Identical preparations were sent to Dr Meyer who considered the evidence as nothing more than contamination or dirt.

The photomicrographs in Heim's monograph are poor, being almost uniformly out of focus and thus do not add much strength to his argument. The article is otherwise a well presented statement of the views of the protagonists of the Robert Meyer theory of serosal metaplasia.

HOOKWORM DISEASE ITS DISTRIBUTION, BIOLOGY, EPIDEMIOLOGY, PATHOLOGY, DIAGNOSIS, TREATMENT AND CONTROL By ASA C CHANDLER, PH D, Professor of Biology, Rice Institute, Houston, Texas. Price, \$5.00. Pp 494, with 33 illustrations. New York: The Macmillan Company, 1929.

"There is probably no important and widespread human disease in which so many important and diversified contributions to knowledge have been made within a decade as has been the case with hookworm disease." To this introductory sentence of the author's preface might well have been added the statement, that among the most important of these contributions stands the long series of articles on almost every phase of the hookworm problem published by Dr Chandler from 1924 to 1929. These researches admirably prepared him for the task of bringing together the recent advances in the knowledge of hookworm disease, which are embodied in a widely scattered, complex and voluminous literature. The work of gathering together and digesting the information from this recent literature has been thoroughly done, apparently nothing of any importance having been missed. The extent of this task is shown by the fact that the author makes direct reference in the text to more than 300 papers published in the last ten years.

In considering these recent researches, Dr Chandler does not hesitate to stress definitely his own opinion on matters of controversy. This does not seem in the least objectionable to the reviewer perhaps because he finds himself in substantial agreement with practically all of the views expressed. In every case, at any rate, the impression is gained that the other side of such controverted questions is given a fair hearing.

The keynote of the whole book is the quantitative consideration of hookworm infestation. This involves emphasis on the worm burden of the population group as measured by some egg-counting method. Much, therefore, is made of the significance of carriers and subclinical infestation and the inadequacy of incidence statistics used alone. While the few who still react against this point of view

will find much to argue against in almost every chapter, the author is correct in saying that he expresses the attitude of most of the recent investigators in this field.

The book surveys in detail every phase of the hookworm problem, giving on the whole an adequate conception of the present status of knowledge. While it would take too long to comment on every chapter, there are certain parts of the book that should be given special mention. The chapter on geographical distribution goes far beyond anything now available in the literature on the relative importance of hookworm disease in different parts of the world. In making his distribution maps, the author has used the knowledge of the factors limiting hookworm dissemination to supplement present knowledge. While, as the author himself states, these maps will undoubtedly have to be modified in detail as new information becomes available, they give by far the best picture at present of hookworm disease as a world problem.

The two chapters on epidemiology give a worldwide view of the relative importance of the influence of climate, soil, race, occupation and human habit on the dissemination of hookworms. While no two workers will agree on every detail of interpretation, this account gives a good idea of present knowledge and should stimulate workers the world over to publish new observations. The detailed account in the appendix of the various methods that have been used in studying the hookworm problem is one of the most valuable parts of the book.

The full bibliography of recent researches for the first time brings together in one place a list of the important contributions to this subject of the last ten years. In citation of references in the text, the book is handled as a monograph rather than a textbook which adds much to its value especially to the research worker.

Although perhaps the text could have been somewhat condensed in places, the book as a whole is written in a clear and interesting style and is unusually free from typographic errors. It ought to go far in giving medical men and parasitologists a better idea of the present status of knowledge on this important disease.

THE IMMUNOLOGY OF PARASITIC INFECTIONS. BY WILLIAM H. TALLERRO, PH.D., Professor of Parasitology, the University of Chicago. Price, \$6. Pp. 414. New York: The Century Company, 1929.

As stated in the preface, this book is a compilation and evaluation of the results of the immunologic work on animal parasites and diseases caused by them. It is the first book of its kind. Chapter 1 reviews the concepts of parasitism, infection and immunity. Chapter 2 is devoted to a discussion of the serologic reactions used in diagnosis in diseases caused by animal parasites: amebiasis, leishmaniasis, trypanosomiasis, etc. In hydatid disease of man and trypanosomiasis of horses complement fixation has reached a high degree of usefulness and promises to become of value also in the human schistosome invasions. In kala-azar, the visceral form of human leishmaniasis, specific serologic tests do not appear to be of diagnostic value, but certain nonspecific tests based on the increase of euglobulin in this disease are giving consistent results. Chapter 3 deals with the lysins and the antibodies that inhibit reproduction of the parasites in trypanosomiasis and bird malaria. Chapter 4 discusses the protective and curative actions of immune serums in certain protozoon infections and trichinosis, and chapter 5 takes up hypersensitiveness and the cutaneous tests for detecting parasitic invasions, more particularly in hydatid disease and ascariasis. In chapter 6 the production of symptoms by animal parasites is considered. The single undoubted toxin produced by animal parasites is the sarcocystin of *Sarcosporidia*. Allergy may play a rôle in parasitic symptomatology. *Ascaris* pneumonia, for instance, appears to be an allergic reaction. In chapter 7, the cellular basis of immunity in parasitic diseases is reviewed, and chapters 8 and 9 deal with the nature and production of immunity in parasitic diseases and with the immunologic reactions for classifying animal parasites. In the appendix is a helpful list of the presumably valid names, com-

mon synonyms and common hosts of the parasites considered in the text. The bibliography 'has been made as complete as possible' and there is an index of authors as well as of subjects.

Taliaferro's book is well written. The presentation is clear, reliable and scholarly. There are remarkably few errors. It reflects credit to the American school of parasitology. The scope and nature of its contents have been set forth in some detail to show its significance to the parasitologist as well as to the immunologist. And the pathologist in the narrower sense can be aided by it in many practical and other ways. It is an important contribution to parasitology and to immunology and will be a stimulus and guide to workers in both sciences.

EPIDEMIC ENCEPHALITIS. ETIOLOGY, EPIDEMIOLOGY, TREATMENT. Report of a Survey by the Matheson Commission. William Darrach, Chairman. Haven Emerson, Frederick P. Gay, William H. Park, Charles R. Stockard, Frederick Tilney, Willis D. Wood, Hubert S. Howe, Secretary. Josephine B. Neal, Director of Survey. Helen Harrington, Epidemiologist. Price \$3. Pp. 849, including bibliography and author and subject indexes. New York: Columbia University Press, 1929.

In this book are recorded the results of a survey of the work on the etiology, treatment and epidemiology of epidemic encephalitis. Closely allied subjects—postvaccinal encephalitis, herpes encephalitis in rabbits—are considered also. Chapter 1 gives a summary of the investigations into the etiology of encephalitis. The chapter concludes as follows: 'In spite of the vast amount of experimental work that has been done, there are still widely varying opinions in regard to the etiology of epidemic encephalitis. A comparatively small group believe that it is a toxic disturbance of the central nervous system. Another rather small group considers that a pleomorphic streptococcus is the cause. A somewhat larger number of investigators are convinced that a filtrable virus identical with or closely allied to the herpes virus is the specific agent. In view of these conflicting opinions many are forced to the conclusion that the etiologic agent of epidemic encephalitis has not yet been definitely demonstrated.' Chapter 2 deals with other types of encephalitis, including the postvaccinal. Chapter 3 reviews the treatment and chapter 4, the longest of all, brings together the epidemiologic data of more than 9000 cases. The strictly clinical aspects and the anatomic changes of the disease are not considered in detail. The bibliography, which is arranged conveniently, takes about half of the book. There is here a highly useful survey which we owe to the generosity of Mr. William J. Matheson, at whose instigation further studies have been started, the results of which will be published from time to time. The reviewer has heard the wish expressed by physicians that competent, minute surveys might be made of the occurrence of epidemic encephalitis during a certain time within definite and suitable localities, the idea being that some light might be thrown on the modes of spread and perhaps other aspects of the disease.

MEDICAL LEADERS FROM HIPPOCRATES TO OSLER. By SAMUEL W. LAMBERT, M.D. and GEORGE M. GOODWIN, M.C. Price \$5. Pp. 331, with 32 figures. Indianapolis: The Bobbs-Merrill Company, 1929.

This is a short resume of the history of medicine in sixteen chapters, the central figures of which are outstanding leaders. Chapter 10, however, on quacks, is an exception to this statement. The emphasis placed on the influence of the leaders whose work is discussed seems fair and adequate, but probably the significance of Claude Bernard as exponent of the experimental method in medicine is not emphasized sufficiently. The warning on page 267, not to call dead bacteria used to prevent typhoid fever a vaccine, is of course a slip, as is also the designation of a certain serum against pneumonia as 'truly antitoxic'. The illustrations reproduce mostly more or less classic engravings and photographs of great medical men. The style is clear, the presentation leans to the semipopular without being

too sketchy and the atmosphere throughout the book reflects the best medical ideals. The authors succeed well in tracing the significant steps in the progressive growth of medical knowledge and its practical application.

PRINCIPLES AND PRACTICE OF ELECTROCARDIOGRAPHY. BY CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Price, \$7.00. Pp. 220, with 61 illustrations. St. Louis: C. V. Mosby Company, 1929.

As one would anticipate, electrocardiography is presented more from the physiologic point of view. Medical students and others desiring an initial acquaintance with electrocardiography may receive adequate instructions in theory and practice from this volume. The clinical features are not neglected. The reviewer is a little disappointed in the fact that although a description of different types of electrocardiographic equipment was included, only indirectly is there any "critique of apparatus" which makes the volume by the same author on the "Circulation of Health and Disease" so valuable to experimenters in this field. Any investigator who is at all interested in experimental pathology of the cardiovascular system and who is not already familiar with recent developments in electrocardiography can readily obtain a background from this volume.

PONTILE GLIOMAS

A PATHOLOGIC STUDY AND CLASSIFICATION OF TWENTY-FIVE CASES *

RICHARD C BUCKLEY, M D

BOSTON

Gliomas of the pons alone or involving together the pons, the adjacent hemisphere of the cerebellum and the cerebellopontile angle are uncommon, if one may judge both from the few cases included in the statistics from neurosurgical clinics and from the individual reports in the literature

In the collection of 1,737 intracranial tumors verified to July 28, 1929, in the Peter Bent Brigham Hospital, 732 were gliomas. Of the latter, 188 were located beneath the tentorium, in the cerebellum and pons, and 25 were classed as "gliomas of the pons, verified, but unclassified."

The number of verified gliomas of the pons does not give the true incidence of these tumors, because patients for whom the diagnosis of glioma of the pons is unquestioned are rarely operated on, and the opportunity of determining the nature of the lesion may not occur. There are twenty-eight such cases grouped as unverified cases of pontile tumor among 782 unverified cases of intracranial tumor.

The problem of classifying these tumors as the gliomas elsewhere in the brain were classified in this clinic by Bailey and Cushing¹ presented difficulties, for from the study of the specimens removed at operation a diagnosis other than that of glioma could not be made. However, as the entire tumors were eventually available for study, it was found possible to classify these gliomas and to demonstrate, despite local peculiarities in structure, similarities in the gross and histologic structure of these gliomas to previously classified gliomas found elsewhere in the brain.

It is the plan in this study to present the majority of these cases and to illustrate the gross lesion, especially. Only the unusual microscopic details will be illustrated, for the microscopic structure of similar gliomas has been thoroughly illustrated in previous presentations from this clinic. Each classified group will be compared with certain known features of similarly classified gliomas found elsewhere in the brain, and it will be seen that these so-called pontile gliomas differ but little from the larger groups of gliomas found elsewhere in the brain.

* Submitted for publication, Sept. 30, 1929.

* From the surgical clinic and laboratory of the Peter Bent Brigham Hospital.

1 Bailey, P., and Cushing, H. A Classification of the Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

MATERIAL AND METHODS

The entire tumor of each patient was available for study. From the formaldehyde-fixed material, paraffin sections were stained with hematoxylin and eosin and phosphotungstic acid hematoxylin after the method suggested by Davidoff.² Frozen sections of the same material were stained with gold chloride sublimate, the Globus³ modification being used, and for oligodendroglia and microglia by Penfield's⁴ combined method.

GLIOBLASTOMA MULTIFORME

One hundred and fifty-two examples of glioblastoma multiforme are included among the 732 gliomas verified in this clinic. These tumors were found to have many features in common in that they were invasive and rapidly growing tumors of the cerebral hemispheres with abundant areas of necrosis, hemorrhage and cyst formation. The great majority occurred in adults of middle age, with but few occurring in young adults. The life history of these tumors was measured in months. The varied histologic character of these tumors has been described by Globus and Strauss,⁵ and Cushing and Bailey.¹

Ten of the twenty-five verified gliomas of the pons were assigned to this group. They were marked by a short duration of life after the onset of symptoms and by a gross and histologic appearance similar in many respects to that of the described previously verified examples of glioblastoma multiforme. There was but one difference in that the age incidence of this small group of cases was the opposite from what was to be expected with present knowledge of the usual age incidence of these gliomas. Whereas these tumors are commonly found in middle-aged patients, seven of the cerebellopontile cases occurred in children and young adults and but three cases occurred in adults of 23, 37 and 59 years of age, respectively.

The onset of symptoms in these patients was commonly with evidence of involvement of the oculomotor nerves or with signs of increased intracranial pressure. Eventually, in the course of the illness, every patient gave evidence of some involvement of the oculomotor nerves as well as of other cranial nerves notably, the sensory division of the trigeminal and the peripheral distribution of the facial nerve. Increased intracranial pressure occurred early in eight of the cases.

2 Davidoff, L. M. Staining Fibrillary Neuroglia in Formalin Fixed Material, *Am J Path* **4** 493 1928.

3 Globus, J. H. The Cajal and Hortega Glia Staining Methods. A New Step in the Preparation of Formaldehyde Fixed Material, *Arch Neurol & Psychiat* **18** 263, 1927.

4 Penfield, W. A Method of Staining Oligodendroglia and Microglia (Combined Method), *Am J Path* **4** 153, 1928.

5 Globus, J. H. and Strauss, I. Spongioblastoma Multiforme, *Arch Neurol & Psychiat* **14** 139 1925.

The interval from the onset of symptoms to the fatal termination was short, averaging but four months. The shortest survival period was one month and the longest seven months. A lesion of the brain stem or of the cerebellum was suspected in each patient because of the multiple cranial nerve paralysis, increased intracranial pressure and involvement of the sensory and motor pathways. Seven of the patients appeared to have such an extensive and inaccessible lesion that an operative procedure was not considered. Suboccipital explorations were made in the remaining four patients in the hope that a tumor of the cerebellum or of the lateral recess would be encountered which could be attacked surgically. However, an early postoperative fatality resulted in each instance.

A postmortem examination of the brain of each patient was made. This gave the unusual opportunity of correlating the clinical symptoms with the lesion and also allowed the assembling of such material that comparison with the gross number of known classified tumors was possible.

The examination of the external aspect of the brain stem showed that in nine of the ten specimens the tumor involved one side of the pons alone or more of one side than of the other side. From one side, the tumor projected into the angle between the pons and the cerebellum to merge with the cerebellum. This part of the tumor never appeared to be enucleable. In two specimens in addition to the lateral extension, there was a projection of the tumor forward to the interpeduncular space and posteriorward to underly the medulla. In every case, the inferior aspect of the pons had a corrugated appearance owing to the fact that the basilar artery and its branches became partially or completely buried in the expanding tumor and thus formed a series of ridges of tumor. Occasionally, one of the cranial nerves, usually the sixth, was strangulated by one of the cerebellar branches of the basilar artery on the side opposite the tumor. In every instance there was involvement of some of the cranial nerves by the tumor, the second, fifth, sixth, seventh and eighth nerves often were surrounded by the tumor or were stretched over the projecting growth. These nerves or their nuclei were either involved by the tumor or strangulated by branches of the basilar artery. This was particularly true of the abducent nerve. In two cases there was evidence in the gross of the tumor's invading the subarachnoid spaces and growing out along the trigeminal nerve to the gasserian ganglion.

Some of the brains were cut in the sagittal, and others in the coronal plane. It was impossible to make out the point of origin of any of these tumors because of the necrosis, hemorrhage, cyst formation and size of the lesion. However, in eight instances the tumor involved one or both sides of the pars basalis and in two it involved only one side.

of the pars dorsalis. In every case, it involved the brachium pontis and one of the hemispheres of the cerebellum. The crus cerebri was extensively invaded along with the pons, in one case, and the medulla oblongata was invaded in four instances. Given a coronal section through a tumor replacing a part of the pons, the brachium pontis and the cerebellar hemisphere on the same side, one would find it difficult to say just where the lesion began.

In every instance the tumor was soft and contained multiple areas of necrosis, small and large hemorrhages and cysts, as well as scattered translucent areas of cellular appearing tissue. The color of the cut surface varied with the necrosis, cyst contents and age of the hemorrhages. In several cases in which the tumor was examined but a few months after the onset of the symptoms, there were apparent lines of demarcation between the tumor and the pontile nerve tracts. However on microscopic examination there appeared to be no line of demarcation. There were varying degrees of dilatation of the third and lateral ventricles, as the fourth ventricle was frequently almost completely occluded by the projection of a cystic part of the tumor or of the entire tumor into this space.

As the clinical histories and gross specimens of these cases compared favorably with those of known verified cases of glioblastoma multiforme so did the histologic appearances. The local peculiarities of structure, especially the crossing of the fiber tracts made the general arrangement of the tumor of the pons differ from that of the tumor of the cerebrum. Areas of degeneration, hemorrhages old and recent and cyst formations were found everywhere. The cells varied in size, shape and preservation. The most common cells were those with oval-shaped bodies and with or without processes. Larger rounded cells and multinucleated cells, with their nuclei variously arranged were abundant. Astrocytes were less common and in no case were there seen fields in which the cells appeared to be differentiating into astrocytes. In the pons, the pattern of growth differed at the periphery because the cells invaded along the course of the nerve fiber tracts (fig 12). This gave a checker-board appearance to the better preserved areas. Elsewhere the necrosis determined the arrangement of the cells. The changes in the blood vessels varied. In the early cases there was but little change while in the instances in which the period of survival was the longest there were just such changes as are described by Globus and Strauss⁵ and Bailey and Cushing,¹ namely, irregular proliferation of the adventitia and occlusion of the lumen by proliferation of cells beneath the endothelial lining.

Any of the ten cases in this group could be considered as material for a single case report because of its many interesting clinical and pathologic features. However seven of the cases are described, each to illustrate either some special clinical or a pathologic observation.

Microscopic descriptions of the individual tumors are not included, as this part of the study is considered in the introduction

The first two cases are examples of glioblastoma of the pons with a short history, two months in all. One case was mistaken for a tumor of the cerebellum and the other for an encephalitis



Fig 1 (case 1) —Glioblastoma multiforme involving the left side of the pons and extending out into the left cerebellopontine angle. A recent hemorrhage has broken through the tumor into the subarachnoid space

CASE 1 —Rapid onset with paralysis of left sixth and seventh nerves. General pressure symptoms. Pseudocerebellar signs and symptoms. Suboccipital exploration yielding no definite evidence of a tumor. Death. Necropsy disclosed tumor of pons.

History—On Sept 18, 1928, Mary O B, aged 6, was referred for observation. The child was normal until seven weeks before admission, when a sudden paralysis of the left sixth and seventh cranial nerves developed. One week later, a staggering gait was noticed. Within five weeks after the onset, signs and symptoms of increased intracranial pressure developed, so that immediate hospitalization was warranted.

Physical Examination—The child was mentally alert. There was paralysis of the left sixth and seventh nerves and involvement of the sensory part of the left fifth nerve. A coarse lateral nystagmus was present. The gait was of the cerebellar type. The deep reflexes were exaggerated. The cutaneous sensitivity

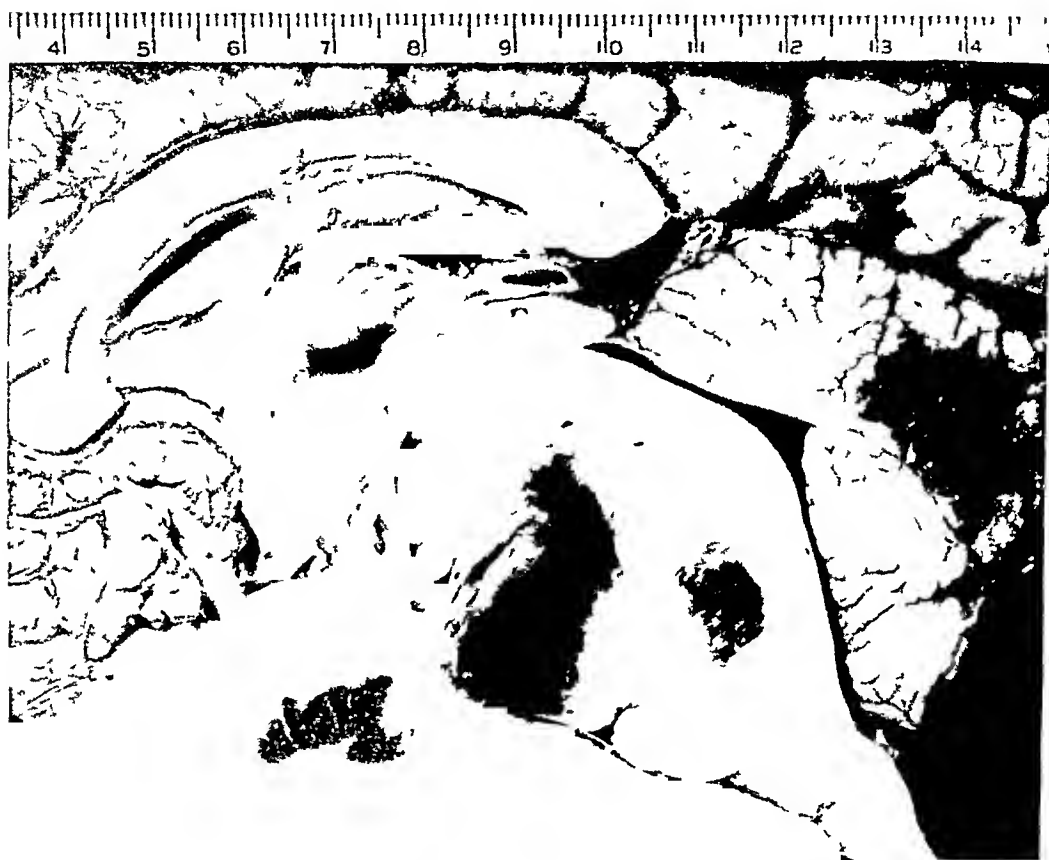


Fig 2 (case 1)—A sagittal section through the tumor seen in figure 1 shows a moderate dilatation of the third ventricle and partial occlusion of the fourth ventricle. The hemorrhages in the tumor are extensive.

over the entire left side was lessened. The optic disks showed a choking of 4 diopters. There were marked hypotonia and ataxia of the extremities.

Course of Illness—A preoperative diagnosis of cerebellar tumor was made. A suboccipital exploration disclosed evidence of increased pressure, but no tumor. Death occurred two days after operation.

Necropsy—A large, soft mass replaced the basilar and part of the dorsalis region of the left side of the pons and extended both into the left cerebellopontile angle, into the right side of the pons and up and under the left cerebellar hemisphere. A recent hemorrhage extended from the middle of the tumor out into

the subarachnoid spaces over the anterior portion of the pons. The tumor was huge, soft, with two large and many small hemorrhages. It presented only occasional small cysts. There was a moderate dilatation of the third and lateral ventricles. The aqueduct of Sylvius was not dilated. The left sixth and seventh nerves were imbedded in the tumor (figs 1 and 2).

Comment—The rapid development of the disease with early symptoms of general intracranial pressure suggested the presence of a tumor in the posterior fossa, probably in the cerebellar hemisphere. How-

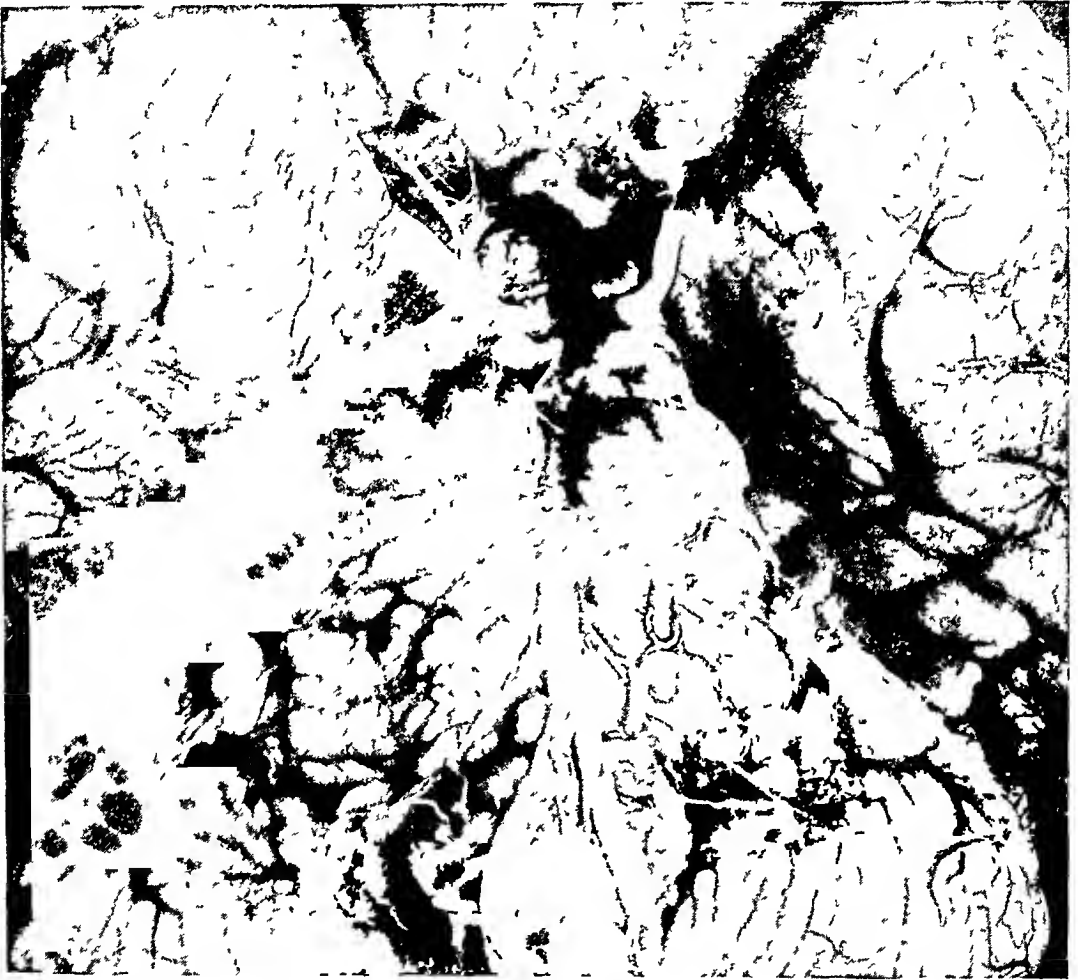


Fig 3 (case 2) —The irregular appearance of the base of the pons is caused by the indentation of a soft glioblastoma multiforme by surface blood vessels. The third and fifth nerves are surrounded by the tumor. The left sixth nerve is strangulated by the anterior inferior branch of the cerebellar artery.

ever, the early involvement of the left sixth and seventh cranial nerves and the sensory tracts on the left side was against the lesion's being in the cerebellum, for such lesions are only occasionally seen in tumors of the cerebellum. The rapid progress of the disease and the immediate cause of death were undoubtedly due to the extensive hemorrhages.

CASE 2—Onset with weakness of left hand Paralysis of left facial nerve Vomiting Dysarthria Dysphagia Spastic paralysis of left side Lateral nystagmus Subtemporal decompression Quadriplegia Death occurred three weeks after operation Necropsy disclosed tumor of pons

Clinical History—On June 29, 1927, Jean S., a 6 year old school girl, was referred with a diagnosis of cerebellopontile tumor Three weeks before her admission, definite weakness of the left hand was observed One week later, left facial paralysis and weakness of the left lower leg developed More acute symptoms began six days before her admission, with dysarthria, dysphagia and paralysis of the right third nerve



Fig 4 (case 2) —This sagittal section of the tumor seen in figure 3 shows the involvement of the pons, medulla and crus cerebri The fourth ventricle is almost obliterated

Physical Examination—There was spastic hemiplegia of the left side and paralysis of the left facial nerve and the right third nerve The right pupil was smaller than the left There was persistent, slow nystagmus of the left eye upward and to both sides There was a positive Babinski reflex and ankle clonus on the left side The optic disks appeared normal

Course of Illness—The great variation in the clinical symptoms suggested to the observers epidemic encephalitis with special involvement in the pons and right crus cerebri The nasal margins of the optic disks showed beginning swelling soon after admission Soon there developed complete quadriplegia, evi-

dence of paralysis of other cranial nerves and severe acidosis. Death occurred on July 27 1927 about seven weeks after the onset of the first symptoms. A complete necropsy was performed.

Necropsy—The pons was irregularly enlarged by multiple, soft nodules, varying in size, which spread in the subarachnoid spaces as far forward as the point of emergence of the third nerves (fig 3). The growth extended far into the interpeduncular space indenting the left uncinate region to involve the right crus cerebri. The basilar artery was almost completely imbedded in the tumor. The sagittal section showed the enormous size of the tumor, which compressed but did not fill the third ventricle (fig 4). It involved almost the entire pons and right crus cerebri and invaded the fourth ventricle. The tissue was soft, necrotic, with multiple small hemorrhages and two large fresh hemorrhages.

Comment—On admission the main physical observation was that of Weber's syndrome with complete paralysis of the oculomotor nerve and complete paralysis of the left side. The extensive involvement of the pons and the right crus cerebri could well explain the Weber's syndrome as the oculomotor nerve went through the growth. With the development of the swelling of the optic disks, a diagnosis of tumor of the pons with extension to the right crus cerebri was made, and an operative procedure was not considered advisable.

The next case represents another of the difficulties in the diagnosis of the subtentorial tumors.

CASE 3—Onset with staggering gait and bilateral ptosis. Dysarthria, dysphagia and rapid development of increased intracranial pressure. Suboccipital exploration for presumed midline cerebellar tumor with early fatal results. Necropsy disclosed tumor of pons and cerebellum.

Clinical History—Bertha P., aged 4, was referred on July 26, 1928, for observation. About four months before the patient's admission, her mother noticed that she staggered and often fell to the right side. At the same time ptosis of both eyelids developed. Dysarthria, dysphagia and the signs and symptoms of increasing intracranial pressure were evident in the month before admission.

Physical Examination—The patient was stuporous. Hypotonicity of all the muscles of the body was noted. The optic disks were swollen to about 5 diopters. Bilateral paralysis of the third nerves and loss of both corneal reflexes were evident. All superficial and deep reflexes were absent.

Course of Illness—It was difficult both to get an accurate history and to make a complete examination of this patient. In the belief that the lesion might be a midline medulloblastoma of the cerebellum, a suboccipital exploration was made on July 30 1926. The midline and fourth ventricle appeared to be filled with tumor. A piece of the bulging floor of the ventricle was taken for histologic section. The child was in poor condition, even before the operation, and died two days afterward. Necropsy was performed.

Necropsy—At the first examination of this brain, the pons was described as a huge, firm mass with the left side appearing smaller than the right side. A mesial section showed the diffuse, symmetrical enlargement projecting into the fourth ventricle. After a second examination the extension of the tumor into the right cerebellopontile angle and the cerebellum was seen (fig 5). This part

of the tumor was soft and necrotic and closely resembled other examples of glioblastoma multiforme. The many nodular projections over the base represented tumor masses growing up between the constricting transverse blood vessels.

Comment—A preoperative diagnosis of midline tumor of the cerebellum, probably medulloblastoma, was made. The absence of nystagmus, the presence of hypotonicity, the increased intracranial pressure and the staggering gait suggested a lesion of the cerebellum located in the midline. This is the youngest patient with glioblastoma multiforme encountered in this clinic.



Fig 5 (case 3)—The basilar surface of this glioblastoma of the pons and adjacent parts is like that seen in case 2. The basilar artery and its branches run in grooves through the tumor. This large, soft tumor extended into both cerebellopontile angles.

Six of the patients with pontile glioblastoma multiforme first complained of staggering gait and falling to one side. In each of these cases, it is most interesting to note that the tumor involved one hemisphere of the cerebellum and the brachium pontis and but a small portion of the pons. In each of these cases, the adjacent cerebellopontile angle was involved.

CASE 4—Onset with paralysis of right fifth and third nerves. Early symptoms of general intracranial pressure. Deafness (right ear). Paralysis of right facial nerve. Left hemiplegia and hemihypesthesia. Suboccipital exploration. Death. Necropsy disclosed tumor of the pons and cerebellum.

History—On Jan 4, 1910, Madeline H, aged 15, was admitted to the Johns Hopkins Hospital as a brain tumor suspect. The patient was normal until five months before admission, when the present illness began with numbness in the right side of the face and drooping of the right eyelid. In rapid succession appeared symptoms of general pressure, ataxia, severe occipital headaches, pain on flexion of the head and left hemiplegia.

Physical Examination—The patient was dull and complained of a stiff neck. The pupils were unequal and nystagmus in all directions was present. Both optic disks were swollen to about 5 diopters. There was an incomplete paralysis of the right abducens and facial nerves. Hypesthesia over the right trigeminal

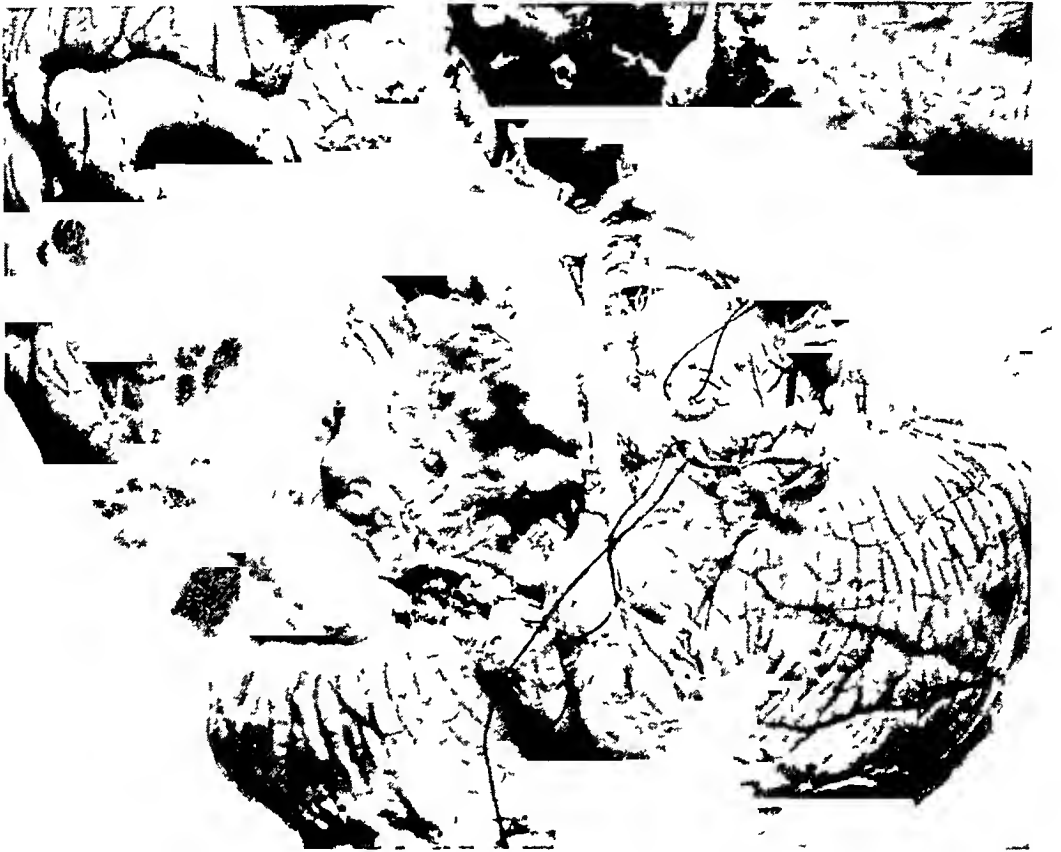


Fig 6 (case 4)—This glioblastoma involved the right side of the pons, grew out into the angle and completely surrounded the right third and fifth nerves. The threads pull apart the left sixth nerve from a branch of the cerebellar artery which had strangulated the nerve.

field and the left side of the body was present. A coarse ataxia and adiadochokinesis were noted.

Course in the Hospital—On Jan 6, 1910, a suboccipital exploration was made, with negative results, and early postoperative death occurred. An examination of the head was made.

Necropsy—The entire right half of the pons was replaced by a large, soft tumor which extended down and back to the level of the olivary body. This tumor filled the entire right cerebellopontile angle and compressed the right cerebellar

hemisphere. On the right side, the cranial nerves from the third to the eighth inclusive were involved by the tumor. On the left side, the sixth nerve only was involved, and this was compressed and flattened by the overlying branch of the left posterior cerebellar artery.

Coronal sections showed a dilatation of the third and lateral ventricles, with the fourth ventricle compressed and flattened by the tumor. The tumor extended into the left side of the pons and also through the right brachium pontis to the right hemisphere of the cerebellum.

The extensive involvement of the entire right side of the pons is shown in figure 6. The cut surface is typical of that of glioblastoma multiforme (fig 7). The multiple cysts, hemorrhages and large areas of necrosis made up the greater portion of the tumor. The subarachnoid space about the tumor was invaded, and the tumor cells surrounded the entire sensory root of the right fifth nerve even out to the gasserian ganglion.

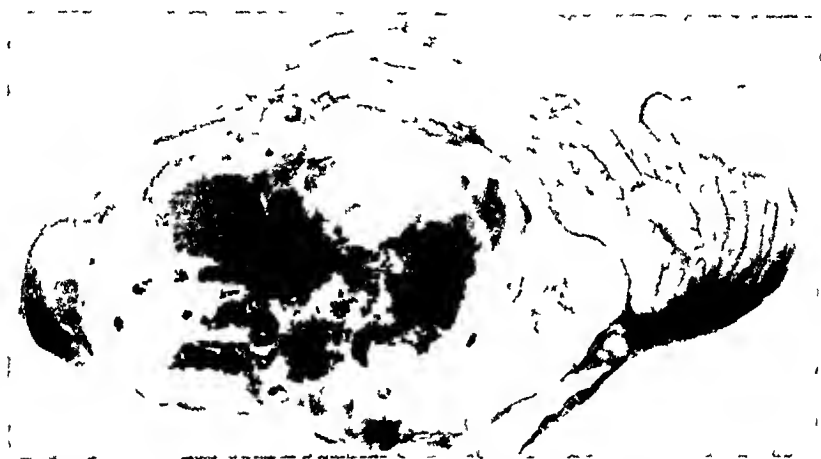


Fig 7 (case 4)—This represents a coronal section through the pons, the cerebellopontile angle and the right cerebellar hemisphere of the brain seen in figure 6. The hemorrhage, necrosis and multiple cysts are typical of this type of glioma.

Comment—From the clinical and pathologic standpoints, this is an excellent example of glioblastoma multiforme of the pons. The pre-operative period of illness was short, and there was evidence of extensive involvement of the cranial nerves on the right side and left hemiplegia and hemihypesthesia. The large soft, infiltrating, degenerated and degenerating tumor with multiple cysts and areas of hemorrhage was typical of other cases in this group.

In his article on strangulation of the nervi abducentes by lateral branches of the basilar artery, Dr. Cushing⁶ included this case as one of the illustrations of the sixth nerve being involved by the stretched artery on the side opposite to the tumor. In this article, attention was

6 Cushing, H. Strangulation of the Nervi Abducentes by Lateral Branches of the Basilar Artery in Cases of Brain Tumor, *Brain* **33** 204, 1910-1911.

also called to the fact that the transverse arteries may cut so deeply into the tissues as actually to lie below the level of the surface. This feature of the tumors is well illustrated in figures 3, 5, 8 and 9.

As in cases 1 and 3, the tumor involved one side of the pons more than the other. The two patients lived for four months and had symptoms of general pressure.

The gross specimen showed the thickened right fifth nerve surrounded by the tumor. The eighth nerve was not found.

CASE 5—Onset with attacks of right internal squint, headache and spasm of muscles of left side of neck. Weakness of left side. Staggering gait. Dysarthria. Diplopia. Symptoms of general pressure. Diagnosis of tumor of pons. No operation. Death. Necropsy.

Clinical History—On Feb 16, 1923, Mary F. aged 13, was referred for observation. The symptoms of the present illness began six and a half months before admission, with transient attacks of right internal squint, slight headache and spasm of the left sternomastoid and trapezius muscles. Six weeks later definite weakness of the left leg and hand were noted. Meanwhile the attacks of torticollis and internal squint became frequent and severe. The patient became drowsy and weak and had a staggering gait, diplopia and dysarthria so that she was hospitalized elsewhere from Oct 2, 1922, to Dec 11, 1922. After discharge she went to school until Jan 9, 1923, then persistent vomiting began and lasted for three days. During the next month, incontinence of urine, inability to swallow and left hemiplegia developed.

Physical Examination—The patient was comatose, and complete left hemiplegia was present. There was bilateral involvement of the fifth, sixth and seventh nerves. The optic disks showed a high grade of choking with secondary atrophy.

Course of Illness—A diagnosis of glioma of the pons was made. Death occurred three days after admission. Necropsy was allowed.

Necropsy—The entire brain stem was distorted by a large, diffuse soft tumor which spread out into both recesses and extended as far forward as the interpeduncular space (fig 8). The tumor involved the right side of the pons and medulla more than the left side. The basilar artery was imbedded in the tumor and ran a tortuous course through it. The branches of this artery disappeared in the tumor. The fifth, sixth, seventh and eighth cranial nerves on either side were difficult to distinguish, as they were imbedded in the tumor. The sections through the pons and medulla showed that the entire right side of the pons and the entire dorsal part of the left side of the pons were replaced by a soft, varicose-colored tumor with multiple cysts and hemorrhages. The tumor involved the medulla and the cerebellum on the right side and jutted up into the fourth ventricle. From many sections it appeared that the dorsal part of the pons was first involved.

Comment—This patient had been in four separate hospitals and was considered as having encephalitis and chronic meningitis. On admission to this hospital, the patient presented the clinical picture of tumor involving the pons and the cerebellum.

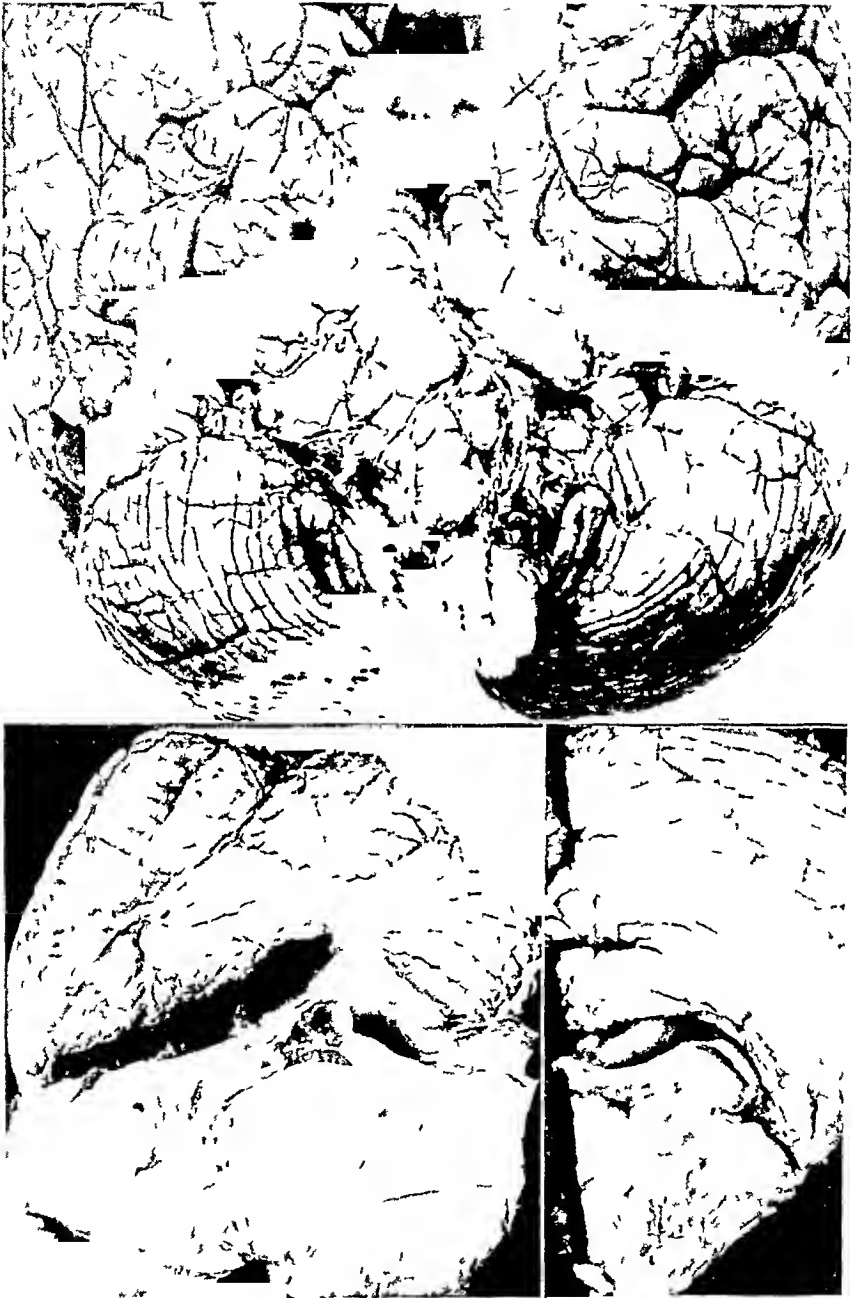


Fig 8 (case 5) —This glioblastoma involves the base of the pons as do the tumors seen in cases 2 and 3. The blood vessels are buried, and the cranial nerves are difficult to locate. The sagittal and coronal sections show a soft, necrotic and cystic tumor surface.

CASE 6—*Bilateral paralysis of the sixth, seventh, ninth tenth and twelfth nerves Quadruplegia Diagnosis of tumor of pons Roentgen therapy with temporary relief Death Autopsy*

Clinical History—On May 2, 1928, Greta L. aged 13 was referred with a diagnosis of tumor of the brain. About ten weeks before the child's admission, the mother noticed that the child held her head retracted toward the right. One week later, a left internal strabismus developed suddenly. Despite this, the patient

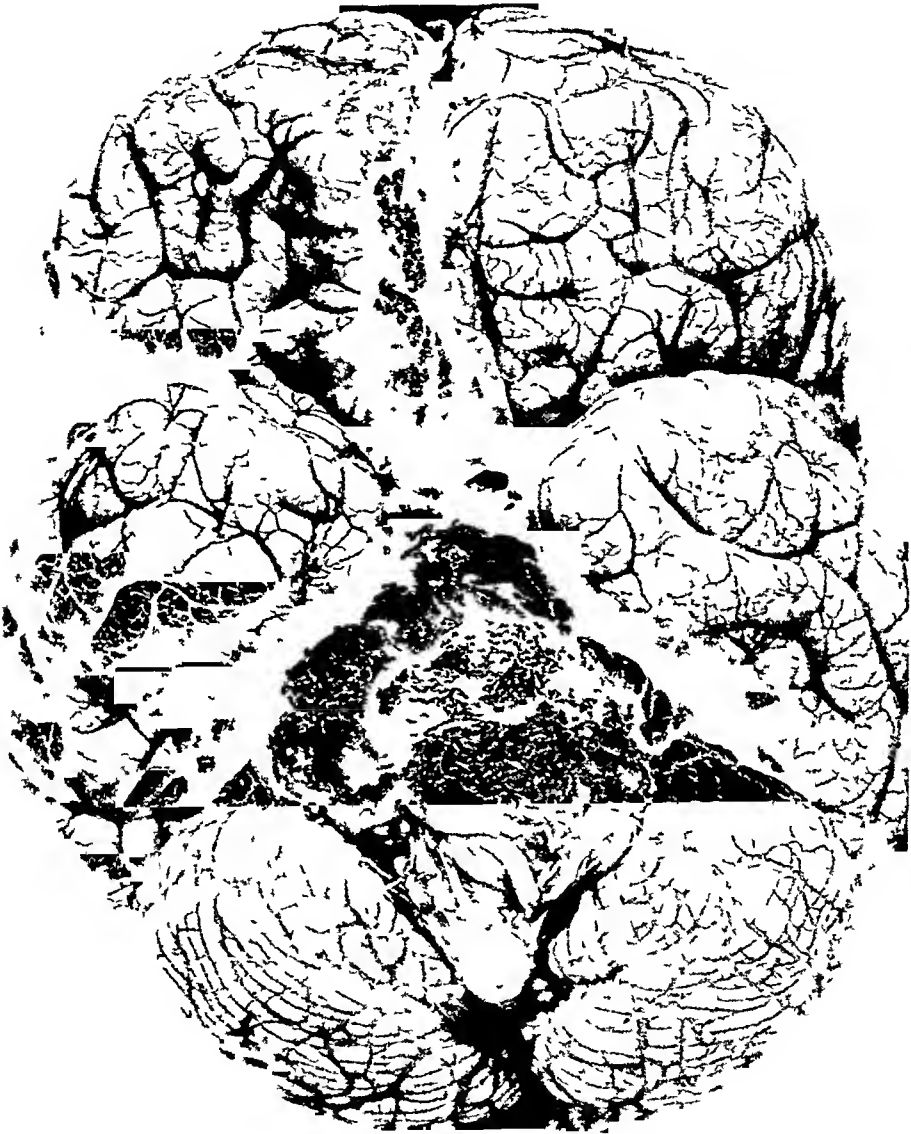


Fig. 9 (case 6)—This large glioblastoma has completely overgrown cranial nerves and blood vessels

continued at school for two weeks, until the sudden onset of a progressive paralysis of the right leg and arm, both sides of the face and tongue. She complained of an occasional occipital headache. There were no symptoms of increased intracranial pressure.

Physical Examination—The child was mentally alert. Right hemiplegia with contracture and paralysis of the left upper extremity was associated with bilat-

eral paralysis of the sixth, seventh, ninth, tenth and twelfth cranial nerves. There was no sensory disturbance. A slight choking of the optic disks was seen.

Course of Illness—A diagnosis of tumor of the pons was made. Several courses of roentgen therapy were given, with temporary relief. Death occurred seven months from the onset of the symptoms. Necropsy was performed.

Necropsy—The entire basilar surface of the pons was covered by a soft, often necrotic, cystic mass which extended into the cerebellopontile angles, forward to the infundibulum and backward to overlap the medulla (fig 9). The basilar artery disappeared into the growth. Many other arteries from the anterior part of the medulla bridged over the space between the tumor and the medulla and disap-

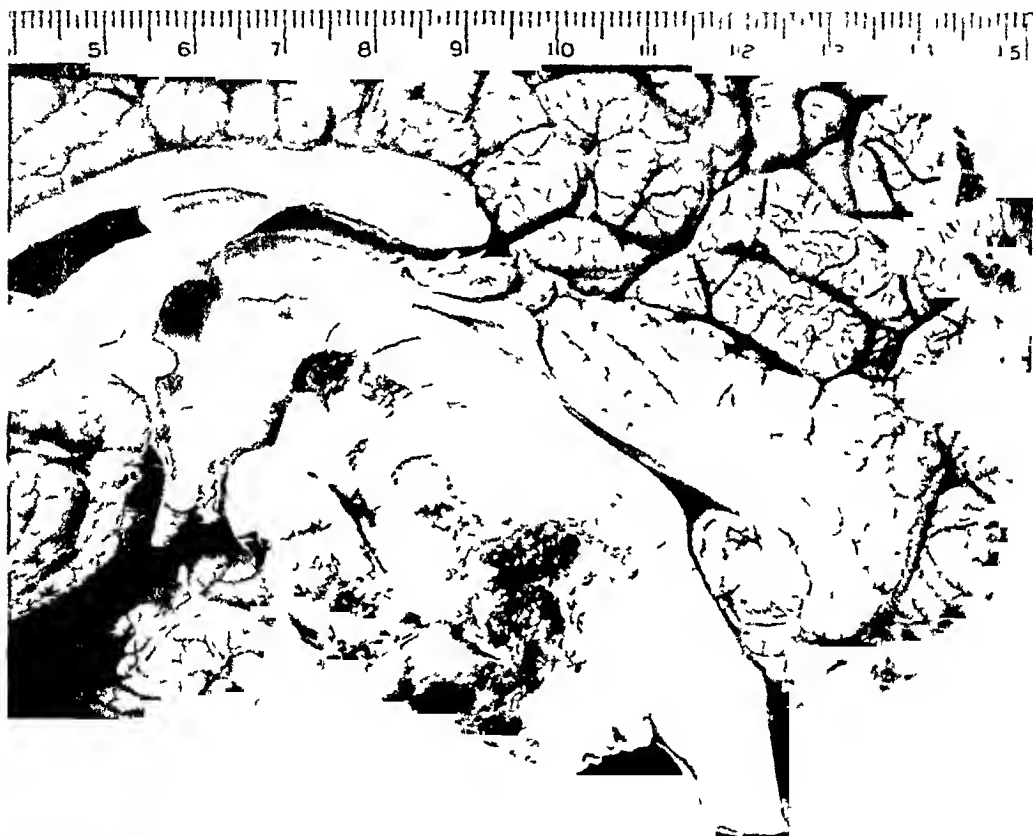


Fig 10 (case 6)—This sagittal section of the tumor seen in figure 9 shows the typical cut surface of the glioblastoma. The fourth ventricle is compressed, and the third and lateral ventricles are dilated.

peared into the tumor. This growth did not adhere to the adjacent cerebellum. By pushing it aside, the fifth and eighth nerves on either side were seen to be uninvolved by the tumor. The third and ninth nerves appeared to be compressed. The other cranial nerves were not recognized. The surface exposed by the sagittal section was an excellent illustration of a glioblastoma multiforme arising from the anterior and basilar portion of the pons (fig 10).

Comment—The diagnosis of extensive glioma of the pons was made because of the involvement of so many of the cranial nerves and of the motor and sensory pathways. The tumor appeared to be the largest

of the series of tumors seen in the region of the pons. The patient was given several courses of roentgen ray treatments and appeared to improve temporarily after each one.

CASE 7—Onset with tinnitus (left) present for four years. Recently, staggering gait. Occipital headaches (left). Nausea, vomiting. Complete deafness, one month. Various hospitalizations. Ataxia. Hyperesthesia, left side of face. Diagnosis of probable left acoustic neurinoma. Suboccipital exploration with finding of tumor of pons filling left lateral recess. Death twelve days after operation. Necropsy disclosed tumor of cerebellum and pons.

Clinical History—On April 1, 1929, Pauline W., aged 37, was referred with a diagnosis of tumor of the left cerebellopontile angle. For four years before

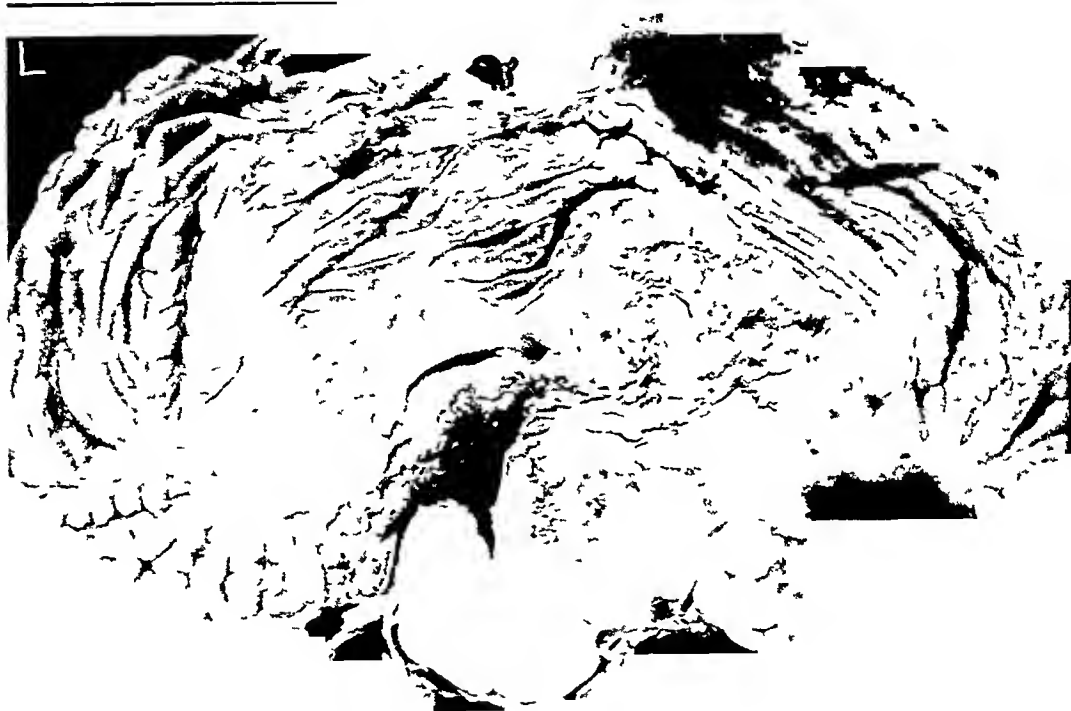


Fig. 11 (case 7)—A part of this large glioblastoma was removed from the right cerebellar hemisphere at operation. The brachium pontis and the dorsal portion of the right side of the pons are involved.

admission the patient had tinnitus in the left ear but no deafness. She was well until four months before admission when staggering gait, increase in severity of a left occipital headache and dizziness forced her to go to bed. Complete deafness in the left ear and tinnitus in the right ear with persistent nausea and vomiting were present for the month before admission.

Physical Examination—The patient was drowsy and emaciated. Nystagmus in all directions was present. There was hyperesthesia over the left side of the face, ataxia of the extremities, especially of the left side and suboccipital tenderness. There was complete deafness in the left ear. The optic fundi showed engorgement of the veins.

Course of Illness—The patient was emaciated, dehydrated and in poor condition. However a suboccipital exploration was begun. As no evidence of a

hydrocephalus was found on tapping the ventricles, the operation was stopped. Ventriculograms were unsuccessful. On the following day, the suboccipital exploration was made, and a glioma of the left side of the pons was demonstrated. A postoperative infection with *Staphylococcus albus* occurred, and death resulted twelve days later. Necropsy was performed.

Necropsy — An infected thrombus was found in the left lateral cerebral sinus. There was a localized meningitis which obscured the structures over the base of the brain.

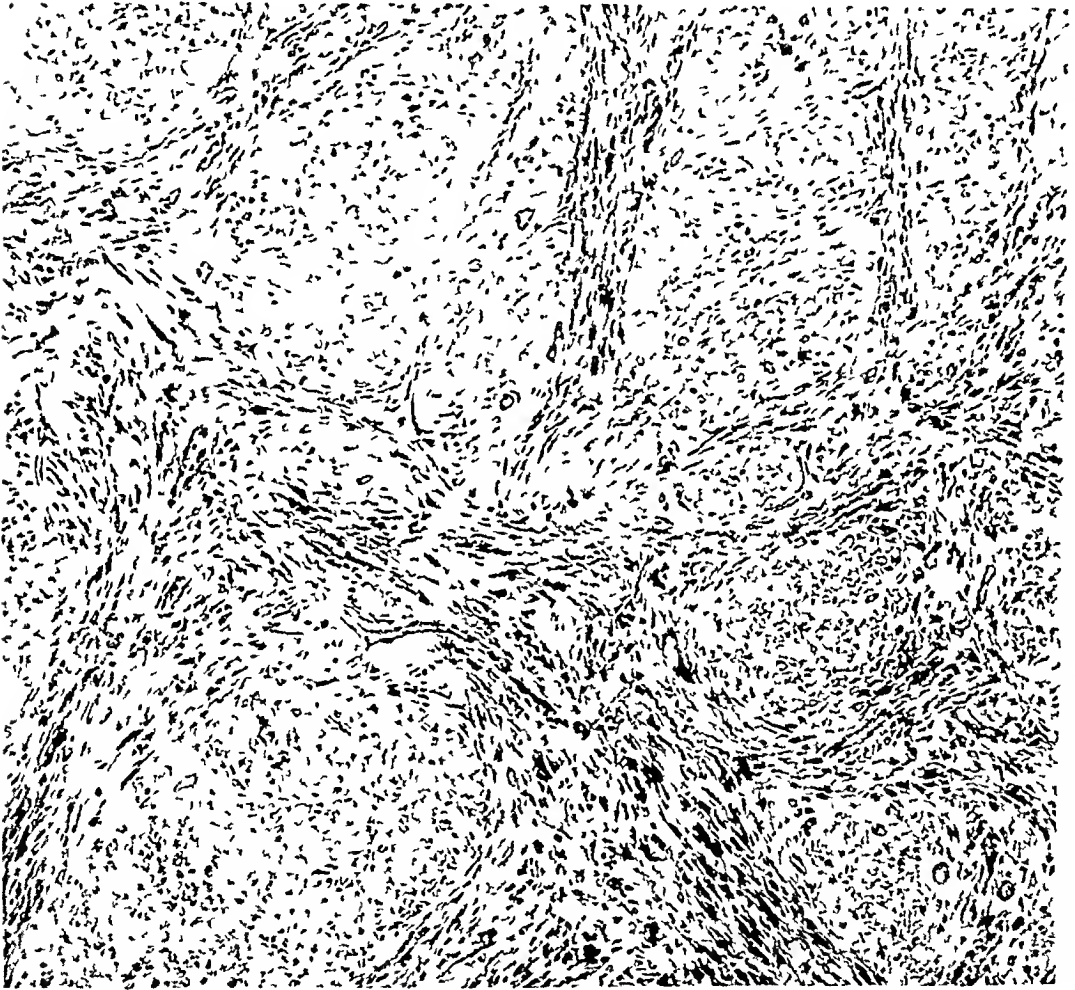


Fig 12 (case 7) — This photomicrograph represents the usual picture at the periphery of the glioblastoma, $\times 100$. It shows the cells invading between the fiber tracts. Phosphotungstic acid hematoxylin used.

The results of the recent operation were shown on the uncapping of the left hemisphere of the cerebellum and a portion of the tumor. There was no distortion of the medulla, pars basalis of the pons or the large basilar arteries. The cranial nerves on the left side appeared normal. On the right side, the eighth cranial nerve was not seen. The right fifth nerve was surrounded by tumor.

The coronal sections showed a soft, partially necrotic, gray-white tumor infiltrating the left pars dorsalis of the pons, the left brachium pontis, the left cerebellar hemisphere and the left side of the dorsum of the medulla oblongata.

(fig 11) The tumor also extended up into the fourth ventricle and partially occluded it. At one point it was adherent to the ependymal lining on the opposite side of the ventricle.

Comment—It is impossible to evaluate the history of tinnitus for four years before the onset of the acute intracranial symptoms. It may be possible that a glioblastoma can be present over a long period of years and then begin to grow rapidly.

The onset with staggering gait, dizziness and headache suggested a tumor of one cerebellar hemisphere. The fact that deafness occurred late in the course and that there were no evidences of papilledema was not in favor of a primary acoustic tumor.

The gross specimen suggests that in this case the growth began in the cerebellar hemisphere and then involved the dorsalis pontis, a part of the pons which has not been commonly found involved by glioma.

SPONGIOBLASTOMA UNIPOLARE

Twenty-four examples of spongioblastoma unipolare appear among the gliomas verified in this clinic. Seven of these tumors were located in the cerebrum and eight in the cerebellum and nine were recently classified from among a group of sixteen verified but previously unclassified gliomas involving the optic chiasm and optic nerves.

Fifteen of the seventeen examples of spongioblastoma unipolare found in the chiasm and in the cerebellum occurred in children under 15 years of age. Six of the seven patients with this type of glioma in the cerebrum were adults.

These tumors are usually slow growing. For this group the average period of survival after the onset of symptoms was over four years. However, the course of illness in five of the eight children with spongioblastoma unipolare in a cerebellar hemisphere was much shorter.

It is of interest that the ages of the five patients herein included were 13, 29, 34, 38 and 59 years, respectively, showing again the contrast in ages seen in comparing the group of patients with glioblastoma multiforme.

There were no special similarities in the clinical histories of the five patients of this group except that two patients were suspected of having acoustic tumor.

The average duration of life from the onset of symptoms until death was two years, with the extremes being four months and four years. Two of the patients were considered as having pontile tumors and were not operated on, while three patients had suboccipital explorations. Two of these patients died shortly after operation and one patient lived for one year.

The tumors were firm and gray with small and large cysts and little gross evidence of necrosis. Usually one side of the pons was

involved, and the tumor tended to grow out into the adjacent angle and downward to invade or overhang the medulla. Consequently, the cranial nerves, especially the sixth, seventh and eighth, were involved on one side.

Although this type of glioma is classified as unipolar spongioblastoma, the cells of the tumor consist of spongioblasts with either one or two processes, as well as of astrocytes in variable number. The cells are variously arranged, either in parallel groups or about blood vessels or areas of degeneration. The cells of the tumors in this series were



Fig. 13 (case 8) —This large unipolar spongioblastoma has grown over the basilar vessels and the cranial nerves.

frequently arranged parallel and appeared to grow down and along the fiber tracts (fig. 14). Small and large cysts were present, and small areas of necrosis were frequent. The cells were often grouped about the smaller areas of necrosis with their processes extending toward the necrotic area.

The histories of three of the five patients with unipolar spongioblastoma will be presented. The clinical diagnoses of these three cases were glioma of the pons, glioma of the cerebellum and glioma of the cerebellopontile angle, respectively.

CASE 8—Onset with emotional disturbances and diplopia Symptoms of general pressure Weakness and paralysis of entire right side Deafness (right) Dizziness Dysarthria Subtemporal decompression Death two months later Necropsy disclosed tumor of pons

Clinical History—On March 14, 1913, Angelina M., aged 13, was referred with a diagnosis of tumor of the brain One year before her admission, the onset of the illness began with diplopia and the symptoms of increased intracranial pressure In the month before admission there was a gradual onset of weakness and paralysis of the right side, deafness of the right ear, dizziness, dysarthria and difficulty in swallowing

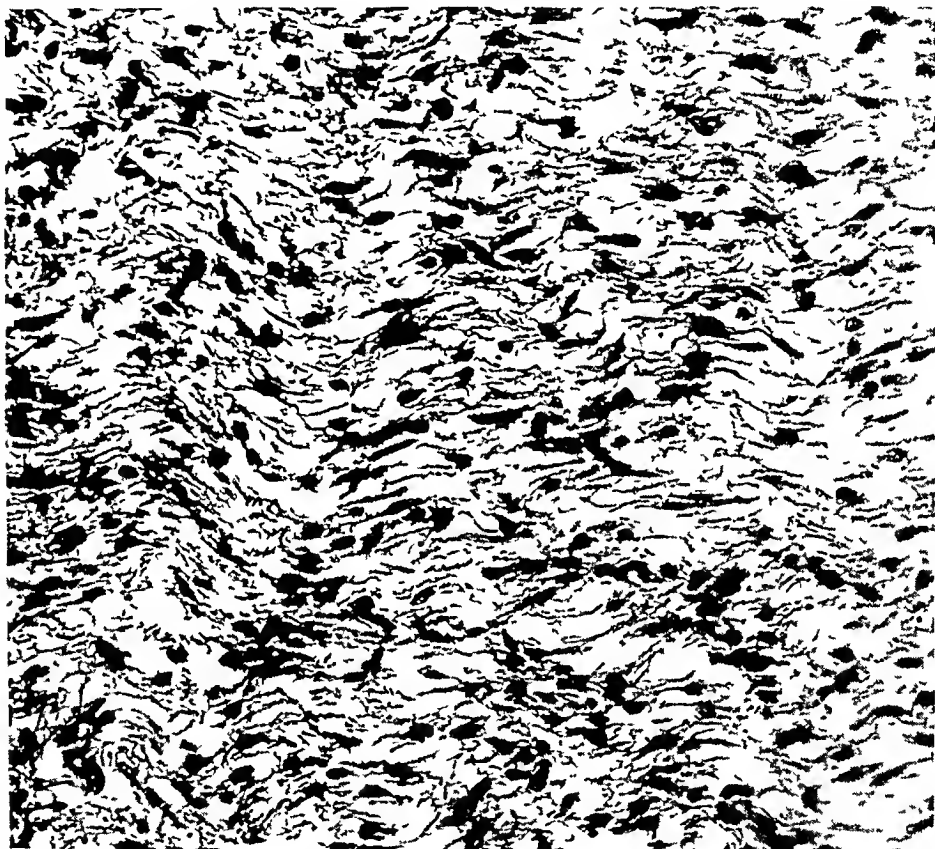


Fig 14 (case 8) —The cells of this unipolar spongioblastoma tend to arrange themselves uniformly in parallel rows, stained with phosphotungstic acid hematoxylin, $\times 600$

Physical Examination—The patient was well nourished There was paralysis of the left abducens nerve and coarse nystagmus of this eye Muscular weakness and anesthesia to touch, pain and temperature of the right side were present The corneal reflexes were absent There was no swelling of the optic disks The patient was completely deaf in the right ear

Course of Illness—A diagnosis was made of tumor of the pons, contraindicating operation After the patient's discharge from the hospital, her symptoms increased in severity, and death occurred in May, 1913, about one and one-quarter years from the time of the onset of the symptoms A partial necropsy was made

Necropsy—The pons was replaced by a firm, gray tumor which invaded the subarachnoid spaces and completely covered the anterior portion of the pons. It extended from the crus above down through the olive. The fourth ventricle was crowded back. This bulky tumor grew down to cover the base of the medulla and filled up both cerebellopontile angles (fig 13). The basilar vessels were imbedded deeply in the tumor.

Comment—This represents another case diagnosed as tumor of the pons and considered to be inoperable. The tumor, as in other examples of this type, extended from the pons to fill out the adjacent cerebellopontile angle.



Fig 15 (case 9)—This unipolar spongioblastoma, as did the tumor in case 8, grew out over the base of the pons to overlie the medulla and fill in the left cerebellopontile angle.

CASE 9—Onset with occipital headaches and blurring of vision. Diplopia. Loss of sensation over right side of body. Presumed tumor of cerebellum. Subtemporal decompression. Suboccipital exploration, with negative results. Death. Necropsy disclosed tumor of pons and cerebellum.

Clinical History—Mrs Preston J. was admitted to the Johns Hopkins Hospital on July 23, 1908, for observation. The present illness began five months before admission with severe occipital headaches and blurring of vision. Two weeks later, diplopia was noted. Three months after the onset, the patient was advised to have her glasses changed to correct her failing vision. There soon developed numbness spreading over the entire right side of the body. There was no nausea or vomiting.

Physical Examination—The patient was well nourished. There was paralysis of the left abducens nerve. The sensation over the right side of the body was impaired, and in addition there was slight weakness of the right hand and arm. A slight swelling of the left optic disk was seen.

Course of Illness—The diagnosis was not clear, and a subtemporal decompression was made on July 24, 1908. There was a steady progress of symptoms with signs of increasing intracranial pressure. Annoying attacks of hiccups, gradual paralysis of the right side, dysarthria and involvement of the right abducens nerve brought the patient back to the hospital. On Oct. 24, 1908, a suboccipital exploration was made, but a tumor was not disclosed. The patient died three weeks later. A partial necropsy was allowed.

Necropsy—The dorsal and basilar portion of the left half of the pons was replaced by a firm, gray-yellow tumor containing many small cysts. This tumor extended into the left cerebellopontile angle and also formed a tongue of tissue over the medulla oblongata (fig. 15).

CASE 10—Onset with paralysis of left sixth nerve and diplopia. Six months later, deafness in left ear, then in right ear. Tinnitus. Paralysis of left seventh nerve. Dysarthria. Staggering gait. Suboccipital headaches. Neurofibromatosis. Diagnosis. Left acoustic tumor. Negative results in suboccipital exploration. Early and sudden fatality. Necropsy.

Clinical History—On June 4, 1919, Elsie T., aged 29, was referred for observation. The illness began about two years before admission with paralysis of the left external rectus muscle and diplopia. About six months later, deafness began in the left ear, and soon involved the right ear. There was no tinnitus. About the same time, twitching of the left facial muscles began, and left facial paralysis developed. Suboccipital headaches, dysarthria, staggering gait and dysphagia appeared during the year before admission.

Physical Examination—Paralyses of the motor division of the left fifth and of the sixth and seventh nerves were present. Deafness was complete in the left ear. There was nystagmus on looking to the left and right. Weakness and hypotonicity of both lower extremities were noted and ataxia of both upper extremities, both more marked on the right side. The Romberg test was positive, and the patient fell to the left. There were generalized subcutaneous neurofibromas over the legs and back and multiple pigmented areas in the skin over the back and neck. Symptoms of general pressure were not present.

Course of Illness—A preoperative diagnosis of acoustic tumor was made, and a suboccipital exploration was undertaken. Internal hydrocephalus was demonstrated, but a tumor was not seen. There was an early postoperative fatality.

Necropsy—The medulla was found to be wedged into the foramen magnum. The pons was enlarged, and in the subarachnoid spaces was a spreading glioma which crossed the median line to involve the fifth to the twelfth cranial nerves on the left side and the sixth nerve on the right side. The coronal sections disclosed a firm tumor replacing the greater part of the left side of the pons and left cerebellar hemisphere and filling in the left cerebellopontile angle. Several recent hemorrhages into the tumor were seen (fig. 16).

Comment—In this patient, the presence of the subcutaneous nodules and pigmented lesions associated with the symptoms and signs of a lesion in the posterior fossa suggested that the tumor was an acoustic neuroma. Neurofibromas and pigmented areas in the skin of the

trunk have been found in a certain number of patients with acoustic neuromas, in patients with gliomas in the region of the optic chiasm and third ventricle and in one patient with a verified fibrillary astrocytoma of the pons



Fig 16 (case 10) —This unipolar spongioblastoma filled out the left cerebellopontine angle and gave the symptoms suggesting an acoustic neuroma. The coronal section shows the basilar artery buried in the tumor.

ASTROCYTOMAS

Astrocytomas are classified as either of the fibrillary or of the protoplasmic type. There are 109 examples of fibrillary and eighty-five protoplasmic astrocytomas among the 721 verified gliomas.

Fibrillary astrocytomas are found with about equal frequency in the cerebellum and in the cerebrum. In the hospital series fifty-two were located in the cerebellum and thirty-eight of these were found in children under 15 years of age. The patients with such a lesion in the cerebral hemispheres were mostly adults.

Protoplasmic astrocytomas are usually found in the cerebral hemispheres only eighteen of eighty-five verified cases having been found in the cerebellum. Fourteen of these eighteen tumors located in the cerebellum occurred in children under 15 years of age. Of the sixty-seven patients with such a lesion in the cerebrum sixty-three were adults.

Both types of astrocytomas are considered to be slow growing with a varying period from the onset of symptoms to the point of hospitalization. Because of the location of the astrocytomas in the cerebellum and because of their occurrence more especially in childhood, more than one half of the patients had symptoms for less than six months before operation the tumors in the remainder going from one to several years before coming to operation.

Both protoplasmic and fibrillary astrocytomas are most commonly found in the midcerebellar region arising from the posterior part of the roof of the fourth ventricle. Of seventy such verified tumors fifty were located in the fourth ventricle and the greater number of these were cystic. The other twenty were located in one or the other hemisphere of the cerebellum and some of them jutted into the fourth ventricle. In the cystic astrocytoma the tumor existed as a mural nodule.

There are nine examples of tumors of the astrocyte type six of which are classified as of the fibrillary type two as of the protoplasmic variety and one as an astroblastoma.

It is of clinical interest that five of these nine astrocytomas were included among the eight tumors suspected of being acoustic which were found among the twenty-five cases included in this report. The special clinical features will be mentioned in the comments on each case.

The six examples of astrocytoma fibrillare were found in patients 9, 12, 14, 28, 42 and 48 years of age. The duration of life from the onset of symptoms until the fatal termination was 6, 8 and 11 months, 2½, 3 and 4 years respectively.

One of these six patients died shortly after admission and four of the other patients died following suboccipital exploratory operations one patient, not operated on, died at home.

The gross lesions in these six cases differed in that four involved the dorsal portion of the pons alone and the tumors were not seen until coronal sections of the pons were made (figs 19 and 21). These

four astrocytomas were not large but their location in obstructing the fourth ventricle resulted in a hydrocephalus and an early fatal result (fig 20). The remaining two examples of fibrillary astrocytoma involved one side of the pons, the adjacent brachium pontis and cerebellar hemisphere and then filled in the cerebellopontile angle on that side. Clinically, these two tumors simulated acoustic tumors.

The cut surface of all the fibrillary astrocytomas showed them to be tough and gray-white, with small cysts and but little opaque, necrotic tissue.

The two examples of protoplasmic astrocytoma occurred in adults 33 and 43 years of age. Both patients were suspected of having an acoustic tumor, and in each, the tumor was found involving the pons, adjacent cerebellar hemisphere and cerebellopontile angle.

The microscopic structure of the fibrillary and protoplasmic astrocytomas showed no differences from that of similar tumors elsewhere in the brain. They were all invasive, and all presented various aspects of necrosis. In the fibrillary astrocytomas, multiple small and large cysts were common. In this type of glioma as in the unipolar spongioblastoma, the nerve fiber tracts showed much less damage than in such gliomas as glioblastoma multiforme. In the fibrillary astrocytoma, in the midst of the tumor, it was possible to find intact nerve cells of cranial nerve nuclei, as well as myelinated and unmyelinated nerve fibers. In the necrosis associated with glioblastomas, fiber tracts were totally destroyed. The reaction to the slow-growing tumors, such as the astrocytomas, was much less marked than that to the rapidly growing, extensively necrotic glioblastomas.

The histories of five patients with either fibrillary or protoplasmic astrocytoma or astroblastoma will be presented.

The tumor in case 1 (fig 17) was one of four examples of fibrillary astrocytoma involving the pons alone. The pars dorsalis appears to be principally involved by this tumor (fig 17). Special involvement of the basilar portion of the pons is illustrated in figure 18.

The remaining cases of fibrillary and protoplasmic astrocytoma and astroblastoma illustrate gliomas involving the pons, adjacent cerebellar hemisphere and cerebellopontile angle. Clinically, the patients with these tumors were suspected of having acoustic tumor.

CASE 11—Onset with paralysis of third nerve. Right hemiplegia. Weakness of right side of face. Symptoms of increased pressure. Exploratory craniotomy with finding of increased pressure. Early fatality. Necropsy disclosed tumor of pons.

Clinical History—On July 27, 1911, Hortense H., aged 12, was admitted to the Johns Hopkins Hospital for observation. Four years before the patient's admission, the parents noticed that the child's left eye was turned up and out. Soon a weakness, followed by paralysis of the extremities of the right side, began.

One year later, a weakness of the right facial nerve was noticed. In the year before admission, symptoms of general pressure were evident. The gait became unsteady. There was no titubus. Despite the previous developments, the child went to school and was able to read well until the time of admission.

Physical Examination—The child was hydrocephalic. Both optic disks were swollen to 4 diopters. There was a paralysis of the right third nerve and facial weakness on the right. There was weakness of the right trapezius and hypesthesia to pain, touch and temperature over the paralyzed right side. The abdominal reflexes were absent. A bilateral Babinski reflex and ankle clonus on the right side were brought out.



Fig 17 (case 11)—The dorsal part of the pons appears to be especially involved by this fibrillary astrocytoma. The fourth ventricle is represented by a mere slit, and there is resultant dilatation of the lateral ventricles.

Course of Illness—Four days after admission, an exploratory operation disclosed ventricular fluid under great pressure. Owing to the development of respiratory embarrassment the exploration was abandoned. Death occurred twenty-four hours after operation. Necropsy was performed.

Necropsy—The pons was asymmetrically enlarged, but the external appearance did not suggest a tumor. A series of coronal sections showed a tumor involving the dorsal part of the pons and obliterating the aqueduct of Sylvius with a resultant hydrocephalus (fig 17). The tumor extended forward to the left side

of the third ventricle and filled the interpeduncular space. It then bulged beneath and into the left optic thalamus to project across the midline to block the right foramen of Monro. The entire tumor was a uniform gray, except for small central yellow areas of degeneration.

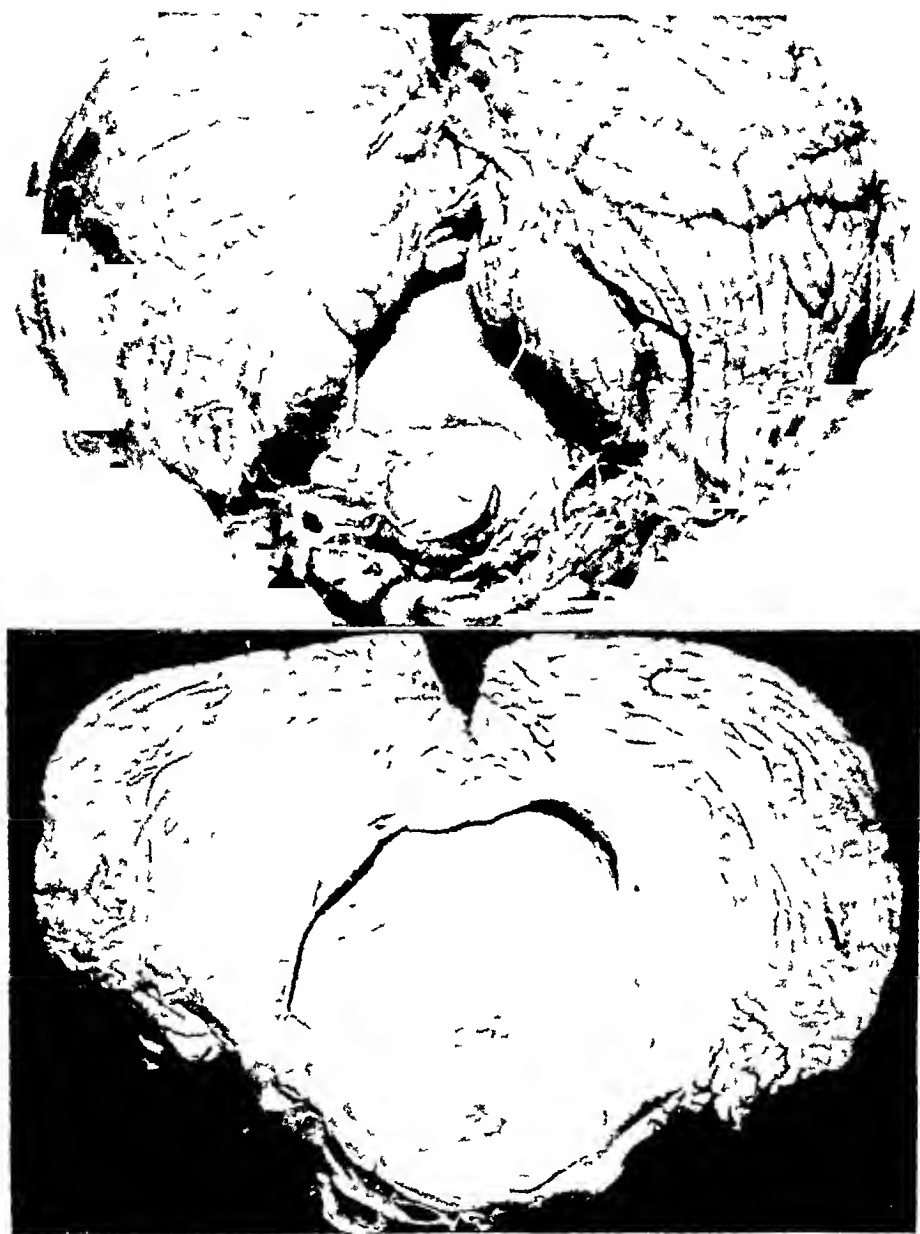


FIG. 18—The diffuse enlargement of the pons by the fibrillary astrocytoma caused a complete occlusion of the fourth ventricle by projecting into it, in contrast to the compression of this ventricle as seen in figure 17. In the upper figure, the solid tumor of the pons is seen to project between the tonsils of the cerebellum.

Comment—This diffuse fibrillary astrocytoma was confined to the pons and invaded the cerebral peduncles. The cerebellum was not involved.

CASE 12—*Gradual but incomplete development of deafness (right) No tinnitus Involvement of right fifth sixth, seventh and eleventh nerves Cerebellar signs and symptoms Suboccipital exploration with exposure of supposed tumor of medulla Death two months later Necropsy disclosed tumor of pons*

Clinical History—On Sept 16, 1927, George G., aged 42, was referred for observation For nineteen years, the patient was aware of the gradual development of deafness, without tinnitus, in his right ear There were no other neuro-



Fig 19 (case 12) —Except for the distortion of the right vertebral and basilar arteries and the fullness of the right lateral recess, a tumor would not have been expected

logic symptoms until two and a half years before admission when numbness of the gums about the right upper molar teeth annoyed the patient to such an extent that he had these teeth extracted The loss of sensation over the area of the fifth nerve spread until the entire right side of the face was numb About the same time, involvement of the right facial nerve was manifested by twitching of the facial muscles Two years before admission, dizziness and staggering gait began The equilibrium of the right leg was especially involved, and he staggered to the right side Several months later daily attacks of vomiting began and lasted

until admission. In the next eighteen months there developed diplopia on looking to the right, a feeling of thickness of the tongue with consequent difficulty in speech, difficulty in swallowing and increased irritability. There was no history of tinnitus or of visual disturbance other than diplopia. Only occasionally were there occipital headaches during a short period before admission.

Physical Examination—The right fifth (sensory division), sixth, seventh, eighth and eleventh cranial nerves were involved. The deafness in the right ear was incomplete. There was a pronounced nystagmus, even at rest, rapid on deviation to the right and slow on deviation to the left. The optic disks appeared normal. The ataxia and hypermetria of the right leg, the positive Romberg test with falling to the right, the staggering gait and the dysarthria suggested a lesion in the posterior fossa, most probably a slow-growing tumor of the cerebellum.

Course of Illness—On Sept. 29, 1927, a suboccipital exploration revealed what appeared to be a tumor of the medulla. After the operation a severe pulmonary



Fig. 20 (case 12)—This coronal section through the fibrillary astrocytoma seen in figure 21 shows the involvement of the pons and cerebellum.

lesion, either an abscess or a necrotizing pneumonia, proved overwhelming and death occurred on Nov. 29, 1927.

Necropsy—The left half of the pons and medulla appeared normal, but the right side of the pons was asymmetrically enlarged by a dense tumor which did not appear to have invaded the subarachnoid spaces (fig. 19). The bulging tumor partly filled the right cerebellopontile angle. The right fifth to eleventh cranial nerves, inclusive, were distorted and out of their normal positions. The coronal sections of the brain stem showed a dense, nondemarcated gray-white finely multicystic tumor, which replaced a portion of both the dorsalis and the basilar portion of the right side of the pons, the brachium pontis and cerebellar hemisphere. The fourth ventricle was compressed and distorted (fig. 20). The fibrillary astrocytes making up the tumor are shown in figure 21.

Comment—There were several facts against the diagnosis of an acoustic tumor. The negative caloric tests and the incomplete deafness and absence of tinnitus made such a lesion improbable, although in

some cases of verified acoustic neuroma the deafness has been found to be incomplete. The absence of the evidence of increased intracranial pressure was a further point against the presence of an acoustic neuroma.

CASE 13—Onset with dizziness. Mastoidectomy followed by facial paralysis on the right. Unsteady gait. Late symptoms of general pressure. Weakness and unsteadiness of the right side. Suboccipital exploration with early fatality. Necropsy disclosed tumor of pons.

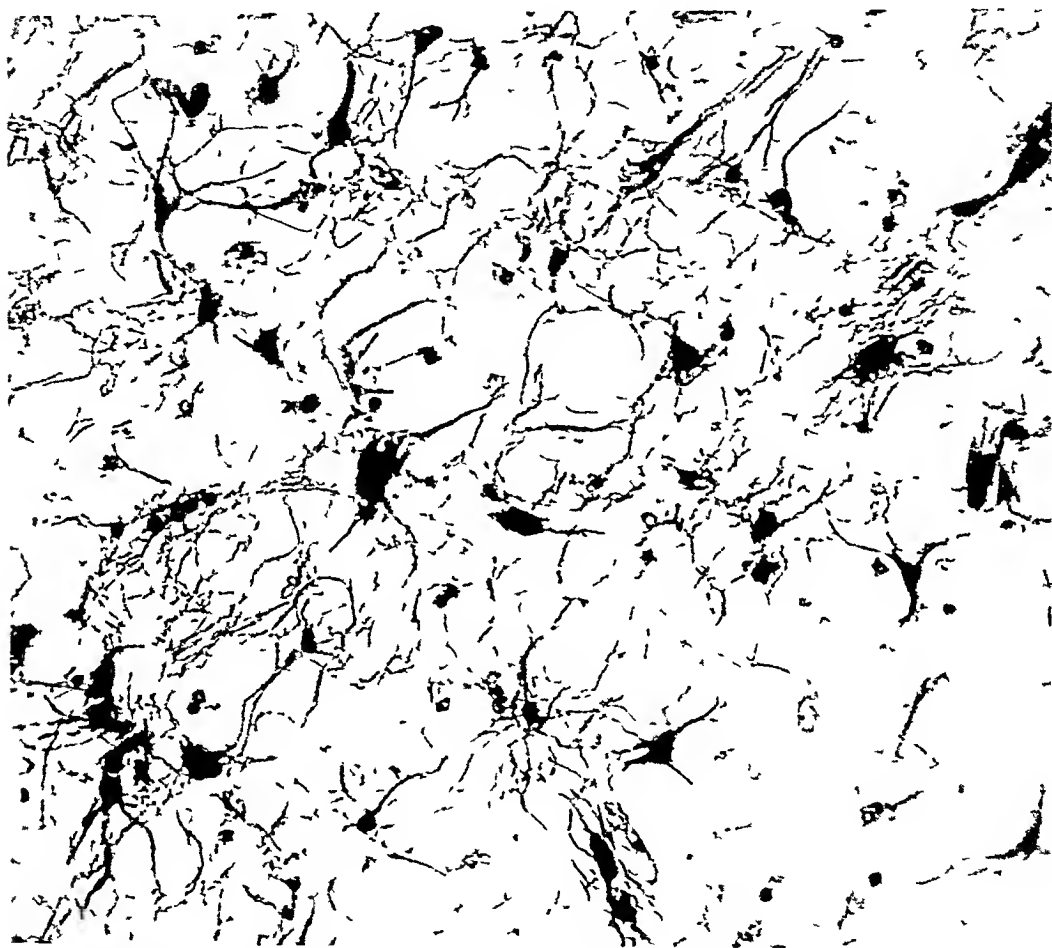


Fig 21 (case 12)—Fibrillary astrocytoma stained with phosphotungstic acid hematoxylin $\times 300$

Clinical History—On May 28, 1915 Carrie P. aged 48 was referred for observation. The illness began in August 1913 with dizziness. After an interval mastoidectomy was performed with no change in the symptoms. Facial paralysis on the right developed soon after this operation. Within a year an unsteady gait complicated the now persistent dizziness and the patient frequently fell to the right side. In the several months before admission there occurred in rapid succession suboccipital headaches, nausea and vomiting, tinnitus (left), weakness and unsteadiness of the right arm and leg, dysarthria and dysphagia. There was no deafness.

Physical Examination—The patient was unable to walk and fell to the right and back when held up. The right pupil was smaller than the left. There was nystagmus in all directions, and a paralysis of the right seventh nerve of the peripheral type and involvement of the sensory portion of the right fifth nerve. Ataxia and dysmetria of the right arm were present.

Course of Illness—A preoperative diagnosis of cerebellar tumor was made. A suboccipital exploration was made on June 2, 1915 and in the right cerebellopontile angle a cyst full of yellow fluid was evacuated. The patient improved remarkably and was discharged able to walk normally and with improved vision. One year later in July, 1916 a severe recurrence of her previous symptoms neces-



Fig. 22 (case 13) —This large, cystic, fibrillary astrocytoma was operated on twice. It filled out the right cerebellopontile angle and invaded the pons and right cerebellar hemisphere.

sitated readmission. The posterior fossa was reexplored, and again a large and similar cyst was found. After the operation, the patient failed to improve, and death occurred on July 23, 1916. Necropsy was performed.

Necropsy —The right cerebellopontile angle was filled with a dense tumor which extended from the right upper lateral portion of the pons and invaded the brachium pontis on the right side (fig. 22). The sections showed a dense gray-white, translucent tissue partially replaced by multiple adjacent small and large cysts filled with gray-yellow gelatinous masses or thin yellow fluid.

Comment—This large, cystic, fibrillary astrocytoma involved the greater part of the right cerebellar hemisphere, the brachium pons and a portion of the pars dorsalis of the right side of the pons. The onset with dizziness, followed by unsteady gait, and the great involvement of the cerebellar hemisphere suggested that this tumor originated in the cerebellum.

CASE 14—*Gradual increase of deafness until complete (1917-1923) No tinnitus Symptoms of general pressure Involvement of right fifth, sixth and sev-*

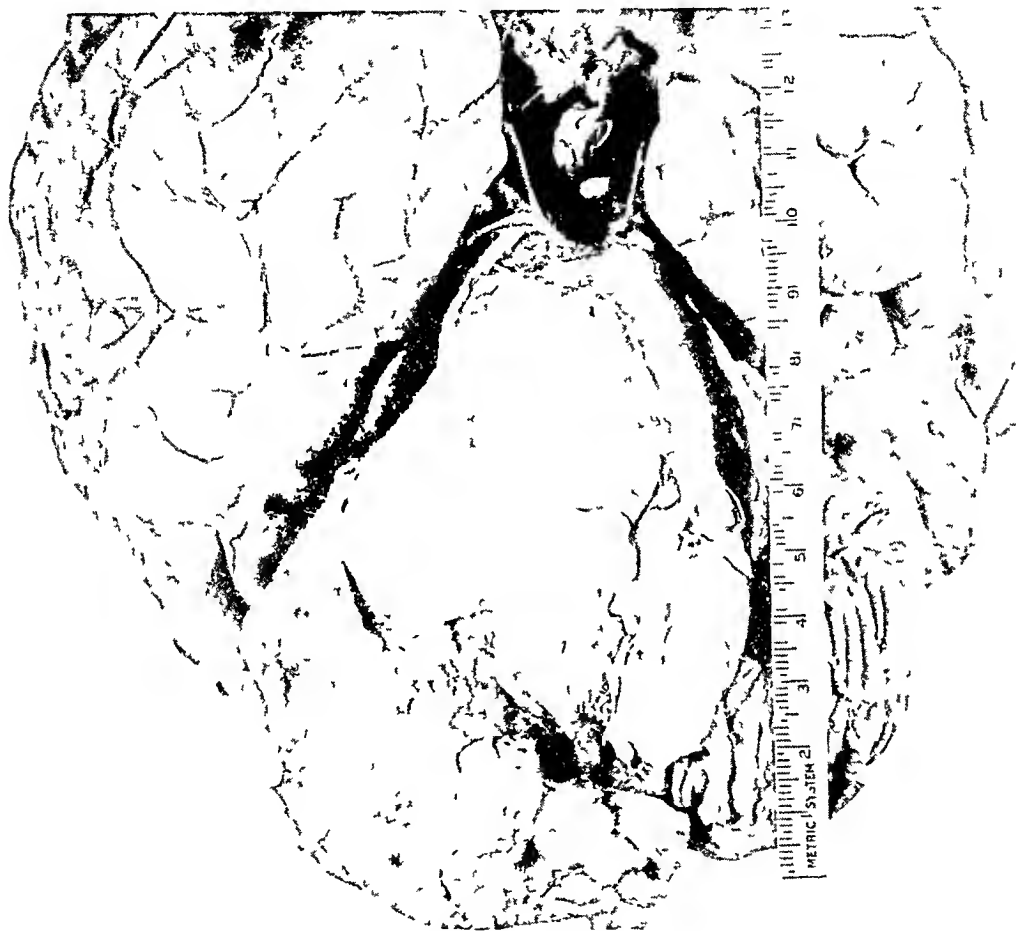


Fig 23 (case 14)—This large cystic protoplasmic astrocytoma was operated on twice. The tumor involved the right side of the pons and the right cerebellar hemisphere.

enth cranial nerves Unsteadiness of gait and staggering to right Cerebellar exploration (1924) for presumed acoustic neuroma with finding of tumor in right lateral recess General improvement Early recurrence of symptoms Second cerebellar exploration, 1926 Temporary improvement Death on June 8, 1927 Necropsy

Clinical History—On Feb 18, 1924 Harold L., aged 33, was referred with a diagnosis of tumor of the brain. The patient realized in 1917 that he was slightly deaf. This condition progressed to complete deafness of the right ear in 1923. There was no tinnitus. Shortly before complete deafness was present, he

had severe generalized headaches followed by dimness of vision and numbness over the right trigeminal field. Unsteadiness in gait was noticed first three months before admission.

Physical Examination—The patient staggered to the right and walked with a wide base. There was a papilledema of 3 diopters on the right and of 5 diopters on the left. A paralysis of the right abducens nerve, a complete loss of sensation over the right trigeminal area and complete deafness in the right ear were found.

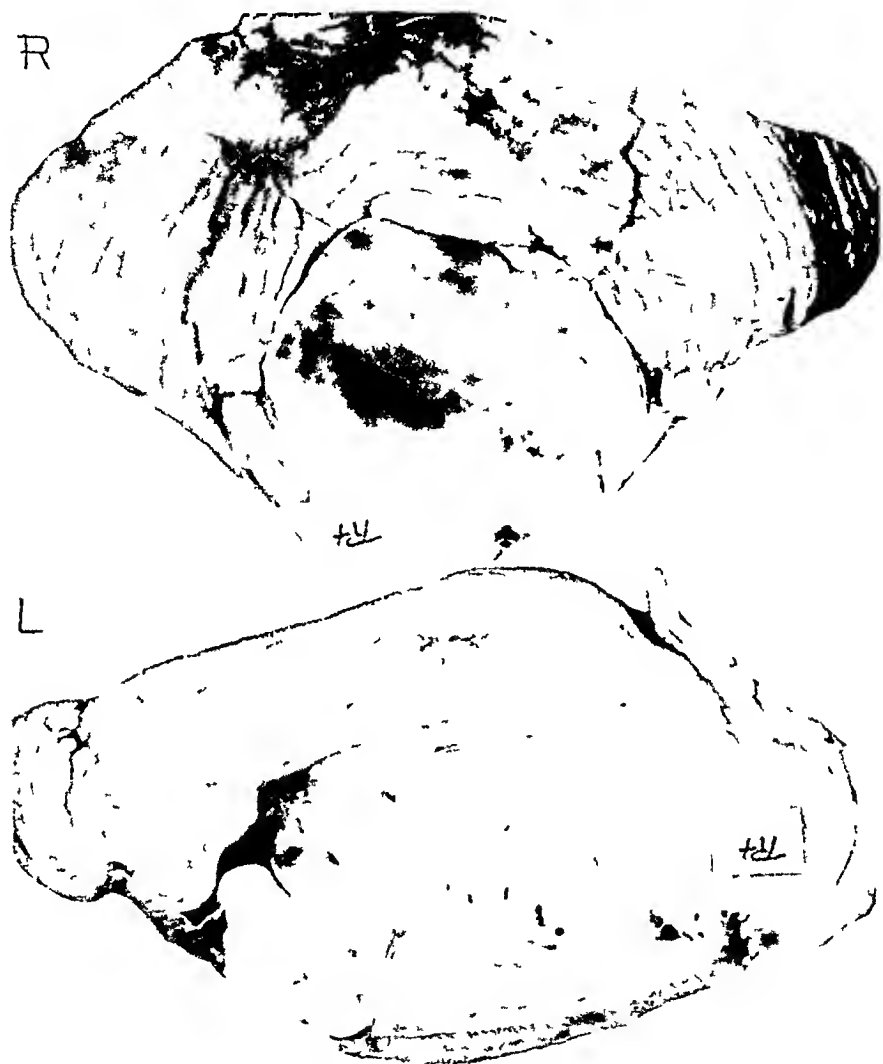


Fig. 24 (case 14)—The coronal sections of the tumor seen in figure 23, show a soft necrotic tumor filling in the fourth ventricle and the adjacent cerebello-pontile angle.

Course of Illness—A preoperative diagnosis of right acoustic neurinoma was made. In suboccipital exploration on Feb. 26, 1924 a soft gray mass was found in the right lateral recess. There was some improvement after the operation, and a series of x-ray treatments was given. The patient was able partially to resume his legal practice until there was a severe recurrence of his previous symptoms, six months after the operation. During the next eighteen months there were fre-

quent exacerbations and partial remissions of the symptoms until the persistent bulging of the decompression area made the patient seek readmission. On April 6, 1926, in a second cerebellar exploration, a large cyst and a dense tough tumor were exposed in the right lateral recess. Again there was a temporary subsidence of symptoms, and the patient was again able to carry on some of his work for the next year until the symptoms of increased pressure made him a bed-patient. Death occurred on June 8, 1927, about ten years from the time the patient first noticed the beginning of deafness.

Necropsy—Necropsy was performed by Dr N Winkleman of Philadelphia. The base of the brain stem was obscured by the large, soft, cystic mass which

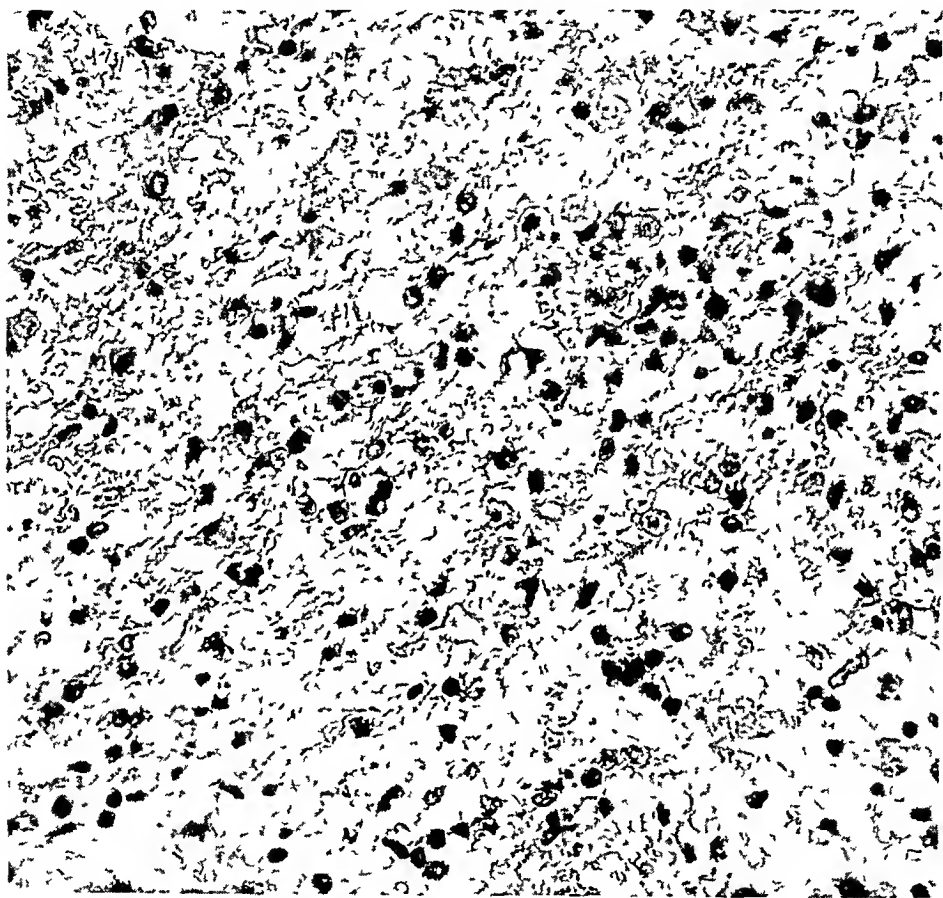


Fig 25 (case 14) —Protoplasmic astrocytoma stained with hematoxylin and eosin $\times 300$

extended over the medulla and filled especially the right cerebellopontile angle (fig 23). The right basilar portion of the pons, the right brachium pontis and the right side of the cerebellum were especially involved by the soft, gray-white tumor in which there were many small hemorrhages (fig 24).

Comment—This patient was supposed without doubt to have a right acoustic neuroma. Although the chronology was correct, the patient was in better physical condition than a patient with an advanced acoustic tumor usually is.

It seemed remarkable that a tumor involving the pons and the cerebellum could exist and produce symptoms for a period as long as ten years. The fact that the patient lived for four years after the first operation illustrates the slow growth of this type of astrocytoma (fig 25)

Among the eight cases of this series of cerebellopontile gliomas causing clinical symptoms and signs suggesting the presence of an



Fig 26 (case 15) —This astroblastoma filled out the right cerebellopontile angle and involved the cerebellar hemisphere more than it did the pons

acoustic neuroma, this was the one considered as the most likely to be a case of acoustic neuroma

CASE 15—Onset with staggering gait, dizziness, ataxia. Soon convulsive attacks (cerebellar type). Involvement of right fifth and seventh cranial nerves. Intracranial aneurysm suspected. Rapid progress of symptoms with development of increased intracranial pressure. Considered as lesion of cerebellopontile angle. Sudden death. Necropsy disclosed tumor of pons and cerebellum.

Clinical History—On Sept 20, 1927, Elizabeth H., aged 59, was admitted for the second time, having been first referred for admission on Aug 11, 1927. The present illness began with a staggering gait about two months before the last admission. Soon numbness of the right side of the face and dizziness developed. Eleven days after the onset, the patient had a sudden convulsion characterized by marked opisthotonic clonic movements of the lower extremities and unconsciousness for twenty minutes.

On the first admission on Aug 11, 1927, there were found a positive Romberg test, ataxia of the right hand and foot and slight deafness. The eyegrounds showed no abnormal changes. It was believed that the patient had had a small hemorrhage from an intracranial aneurysm, and she was discharged five days later, untreated.

In the five weeks' interval to the second admission, the patient had had seven recurrent convulsive attacks. Complete facial palsy on the right and difficulty in



Fig 27 (case 15) —The coronal sections of the tumor seen in figure 26 show a soft necrotic tumor filling in the fourth ventricle and the adjacent cerebellopontine angle.

speech and swallowing developed. Persistent nausea and vomiting were present the three weeks before admission.

Physical Examination—There was evidence of recent loss of weight. Both optic disks showed a choking of from 4 to 5 diopters' elevation on the right and of 2 diopters' elevation on the left. There was complete deafness in the right ear. The caloric tests indicated a nerve lesion on the right. Complete facial palsy on the right of the peripheral type and involvement of the sensory division of the right trigeminal nerve were found. Persistent nystagmus, coarser to the right, gross dysarthria, marked ataxia and hypermetria in the right hand and leg, stiffness of the neck and right suboccipital tenderness were additional observations.

Course of Illness—It was believed that a lesion of the right cerebellopontine angle was present. Two days after admission, while being prepared for operation, the patient suddenly had respiratory failure and died.

Autopsy—An examination limited to the head was made. In the right cerebellopontile angle was the surface extension of a soft yellow tumor involving both the pons and the right hemisphere of the cerebellum. The fifth, seventh and eighth cranial nerves on the right side were embedded in tumor (fig. 26).

The coronal sections through the cerebellum and brain stem showed a large, soft, nonencapsulated tumor replacing the ventral portion of the right hemisphere of the cerebellum filling up the greater part of the right cerebellopontile angle and invading the right lateral portion of the basilar arch of the pons (fig. 27).

The microscopic sections showed it to be an astroblastoma.

Comment—This represented the eighth case of the twenty-four in this series considered as cerebellopontile angle lesions, resembling acoustic neuroma. However, there were many facts against this lesion's being an acoustic neuroma. The short course of the illness suggested a metastatic lesion to the brain, but on examination there was no evidence of a primary focus. The fact that staggering gait, ataxia and dizziness were the early symptoms and that deafness occurred relatively late in the course suggested that the lesion began in the cerebellum and involved the cerebellopontile angle later. The repeated convulsive attacks with rigid neck, unconsciousness and opisthotonic and clonic convulsions of the extremities suggested a cerebellar lesion and also a rupture of an intracranial aneurysm.

From the examination of the gross lesion it would seem that the tumor began in the ventral portion of the right hemisphere of the cerebellum, grew to fill out the angle and then involved only the lateral area of the basilar portion of the right side of the pons.

COMMENT

This study was made for the purpose of classifying these gliomas of the pons and of the pons and cerebellum, and a discussion of the clinical symptoms will not be presented.

Horrax⁷ analyzed the clinical observations of fourteen patients of this group of pontile gliomas and called attention to the frequent involvement of the cranial nerves, especially of the oculomotor group, both at the onset of the illness and during the course of it. He also commented on the frequency of pseudocerebellar signs and symptoms but the study of the gross specimens of these tumors indicates that these clinical manifestations were due to the involvement of the cerebellum.

Eight of the patients with pontile gliomas were suspected of having tumors of the acoustic nerves, and in each there was found a glioma involving a portion of the pons and the adjacent cerebellar hemisphere and filling in part of the cerebellopontile angle. A correlation of the

⁷ Horrax, G. Differential Diagnosis of Tumors Primarily Poneal and Primarily Pontile, *Arch Neurol & Psychiat* **17** 179 1927.

clinical and pathologic observations in these patients will form a separate communication from Dr. Horrax and myself.

Pathology—Although these tumors were considered as "gliomas of the pons" for statistical and localizing purposes, it was found from the study of the gross specimens that in but four instances was the pons alone the site of the tumor. In each of these four instances the tumor was a fibrillary astrocytoma involving the pars dorsalis of the pons and either compressing the aqueduct of Sylvius and the fourth ventricle or actually growing up into the fourth ventricle; the pons was symmetrically enlarged and a tumor would scarcely have been suspected from the external appearance.

In the remaining twenty gross specimens the tumor involved one or the other side of the pons or both and the adjacent brachium pontis and hemisphere of the cerebellum. In all these specimens, the tumor filled in one or the other cerebellopontile angle and clinically many of the patients were considered as having tumor of the cerebellum or tumor in the cerebellopontile angle.

The gross structure of the gliomas considered varied with their type. All the examples of glioblastoma multiforme and the one of astroblastoma were large, soft tumors with many areas of necrosis, hemorrhage and cyst formation. These tumors involved the base of the pons especially. Consequently the basilar artery and its branches were embedded in the soft growth and the brain stem was given a corrugated appearance. The ten examples of glioblastoma multiforme and the one of astroblastoma represent the only examples of such types of glioma found in the brain stem or cerebellum among all the varied tumors observed in this clinic. There would seem to be no reason why such gliomas should not be located in either the pons or the cerebellum.

The unipolar spongioblastomas and the fibrillary astrocytomas were small, tough, invasive tumors containing cysts of varying size and they were altogether different in their gross appearance from glioblastoma multiforme.

Histologically these tumors showed no essential differences from similarly classified tumors seen elsewhere in the brain. The sections taken from the periphery of the tumor in the pons gave a confusing picture because of the interlacing of the fiber tracts. The cells of glioblastoma multiforme and spongioblastoma unipolare tended to grow along the tracts.

In the central portions of the rapidly growing glioblastomas the necrosis of the nerve tracts and ganglion cells was such that none or little of these tissues was left. In contrast the study of the central portions of the slower growing gliomas in this group showed some intact nerve fibers, axis cylinders and ganglion cells. The tumor cells

could be seen invading the perineural spaces and undergoing mitosis there at the advancing edge of the glioblastomas. Intact ganglion cells were often seen surrounded by the infiltrating astrocytoma and spongioblastoma unipolare.

The reaction of the brain toward the invading tumors differed. At the periphery of the rapidly growing glioblastoma and at that of the one astroblastoma, with all of the necrosis and hemorrhage, there was seen such a collection of advancing microglia in the cerebellum as to make one think of a tumor of these cells. The usual and well known changes of these cells into phagocytic cells were clearly followed. There was a much less marked response on the part of the fibrillary astrocytes. The small blood vessels in the uninvaded tissue at the periphery of these tumors frequently showed an increase in number as well as an increase in mitoses in the cells in their walls. This proliferation of cells beneath their lining often resulted in almost complete occlusion of the lumen.

The reaction of the microglia about the periphery of the astrocytoma and that of the unipolar spongioblastoma was much less marked. At the edge of the protoplasmic astrocytoma, the cells of the tumor were so mixed with a response on the part of the fibrillary astrocytes that a mixed tumor appeared to be present.

The origin of a tumor which involved the pons, brachium pontis and cerebellum could not be demonstrated in any of the gross specimens. However, in correlating the clinical and anatomic observations it was interesting to note that in the six patients giving as their first symptom staggering gait the lesion involved one cerebellar hemisphere extensively and the adjacent portion of the pons less extensively. In the patients giving as their first symptom evidence of involvement of some of the cranial nerves, the lesion was extensive in the pons as well as in the adjacent cerebellar hemisphere.

SUMMARY

A group of tumors involving the pons and the cerebellum previously unclassified have been classified as are the other gliomas verified in this clinic.

Although grouped as pontile gliomas, only four of these tumors were found to involve the pons alone; the remaining twenty-one involved the pons, brachium pontis and the adjacent cerebellar hemisphere and cerebellopontile angle. The origin of this larger group involving the cerebellum and the pons could not be demonstrated from the gross examination.

Ten of the twenty-five tumors were classified as glioblastoma multiforme. Here the average duration of life from the onset of

symptoms to the fatal termination was but four months. Each of the tumors was large, soft and necrotic, with many hemorrhages and cysts. The basilar vessels and cranial nerves were often buried in the soft expanding tumor. The histologic structure of this rapidly growing type of glioma was similar to that found in glioblastoma multiforme of the cerebral hemispheres, except that at the periphery of the tumor the pattern of growth was modified by the invasion along the fiber tracts.

The one example of astroblastoma proved to be the only instance of such a lesion to be found in the brain beneath the tentorium.

Fourteen of the gliomas were slower growing tumors and were classified as protoplasmic, as fibrillary astrocytoma or as spongioblastoma unipolare. The gross and histologic structure of these tumors was similar to that of such tumors found elsewhere in the brain.

The average duration of life of patients of this group from the onset of symptoms to the fatal termination was two years, the extremes being four months and four years.

The reaction of the brain against the advance of tumor varied in degree. The response of glial elements, microglia, connective tissue and blood vessels was greatest at the periphery of the glioblastoma multiforme and least at the edge of the slower growing astrocytoma and spongioblastoma unipolare.

A CONGENITAL CAPILLARY ANGIOMA OF THE PAROTID GLAND

CONSIDERATION OF SIMILAR CASES IN THE LITERATURE

JOSEPH MCFARLAND M.D.

PHILADELPHIA

While I was visiting Grace Hospital, Detroit Dr. Clarence J. Owen showed me a tumor of the parotid gland removed by Dr. Frank J. Kelly and received in the hospital laboratory for study and diagnosis. I recognized it as rare and interesting and since I was known to have written on tumors of the region Dr. Owen kindly presented it to me. I now place it on record with the full permission of Dr. Kelly and Dr. Owen.

REPORT OF CASE

History—R. L. H., a white boy, aged 5 months at birth, was found to have a swelling "on the left side of the face, primarily back of the angle of the jaw. It increased slowly until the fifth month, then it grew larger rapidly "and extended over the angle of the jaw." It was regarded as a malignant tumor and the patient was brought to the hospital for operation on March 4, 1929. At that time, the skin covering the area was 'contracted,' and the appearance suggested "a cystic disturbance below." There was no discoloration of the skin nor was there any vascular nevus on or about the swelling.

The operation resulted in the exposure and removal of a flattened, well encapsulated mass measuring approximately 6 by 6 by 3 cm.

The child quickly recovered from the operation and the wound healed nicely. The last examination was made about Oct. 1, 1929, nearly seven months after the operation, when the patient appeared to be well and showed a normal gain in weight.

Though seven months is a short time in which to conclude the history of any tumor, there is good reason to suppose that this was a benign disturbance of a kind not marked by recurrences, so that there is no reason to postpone further the report of the case.

Gross Appearance—The general shape of the tumor was circular, slightly flattened and thicker at the middle than at the edges. It was enclosed in a fairly smooth, rather tough capsule. When cut across the greater diameter and then in several other directions, it was found to be of the same consistency and grayish-pink throughout except that a few areas showed a darker reddish tint. There were no cysts or necrotic areas.

Submitted for publication, Nov. 13, 1929.

From the McManes Laboratory of Pathology of the University of Pennsylvania.

The tissue was distinctly lobulated, the lobules being but a few millimeters in diameter and slightly separated from one another by narrow bands of vascular areolar tissue, and meeting one another by flattened surfaces so as to have numerous sides and various blunt and sharp angles. It thus exactly resembled the parotid gland, the only notable difference being the great size of the removed mass. It was more like a hypertrophy of the gland than a tumor.

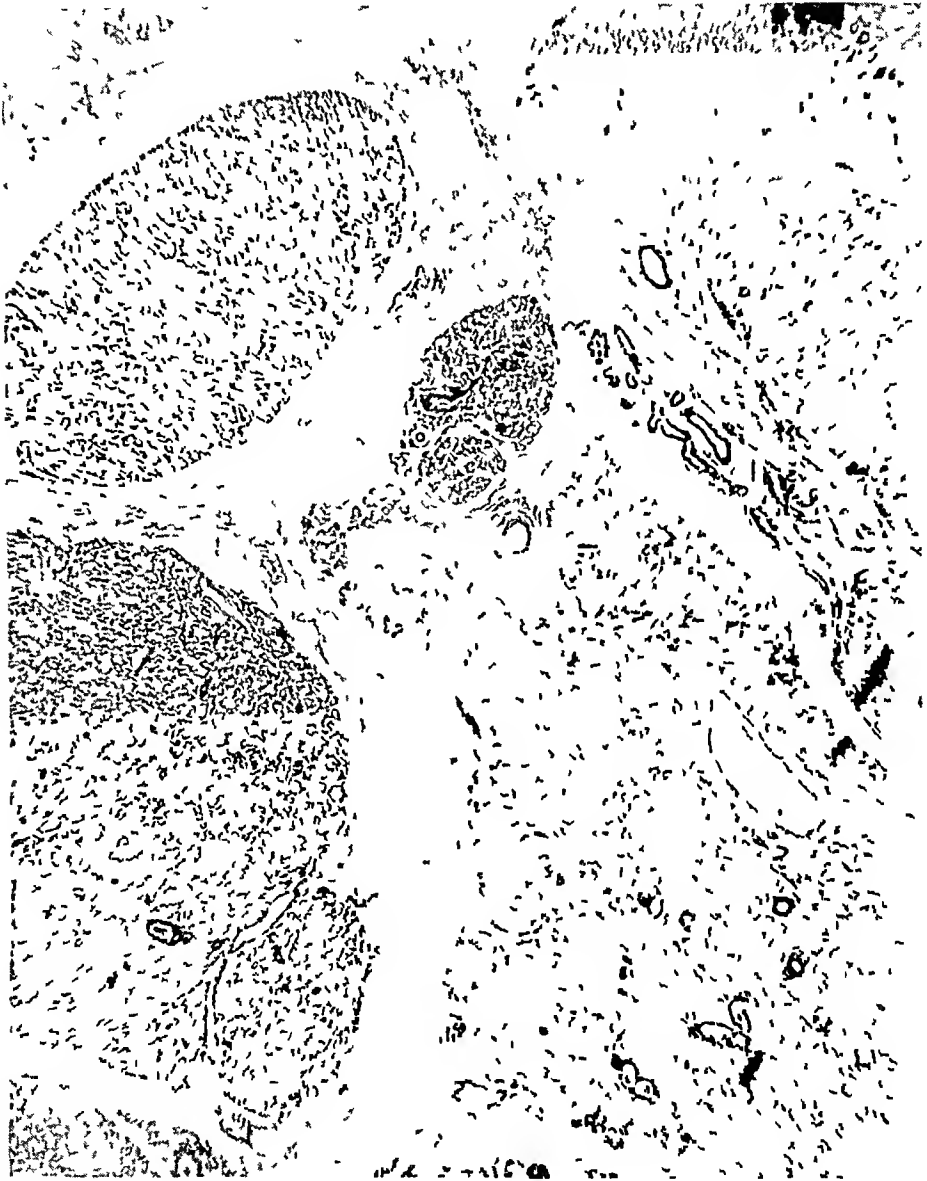


Fig 1—The lobular structure of the tumor is shown. Small ducts can be seen in the lobules and larger ones between them.

Microscopic Examination—Sections from various parts of the lesion were cut in paraffin, stained and examined. Under low magnification, the tissue showed a fairly uniform texture divided into larger and smaller lobules by intermediate bands of fibrillar tissue. An increase in the magnification (fig 1) gave the impression that the tissue was a gland with compact acinous tissue forming the lobules and with a duct system composed of smaller elements in the lobules

and larger ones between them. Scattered elements near the center of the illustration indicated that the organ was a racemose gland.

Observation under a still higher power, as in figure 2, yielded a surprise. The field shown in this illustration was from one of the larger lobules, near its central part. In the center there was a duct, the epithelial lining of which seemed to be made up of an excessive number of crowded cells. But about it, where the acini



Fig 2—A higher magnification of one of the lobules, showing a duct in the center. There is no glandular tissue, the whole lobule is made up of vascular tissue.

of the parotid gland should have been, there was a new tissue made up of small blood vessels, in many of which the red corpuscles could be distinctly seen. If the slide was moved so as to shift the field of observation toward the periphery of the same lobule, the vessels became both more numerous and larger. Scarcely anything other than vascular tissue could be discovered. Study of numerous sections from various parts of the lesion led to the impression that throughout

the entire parotid gland, probably prior to the period of its anatomic perfection the vascular tissue adopted an abnormal vegetative activity that resulted in an excess of capillaries at the expense of the glandular tissue, most of which did not develop while the remainder became so crowded and compressed by the vessels as to be unrecognizable except as scattered individual cells among the capillaries with shapeless groups of cells here and there, as shown in figure 3

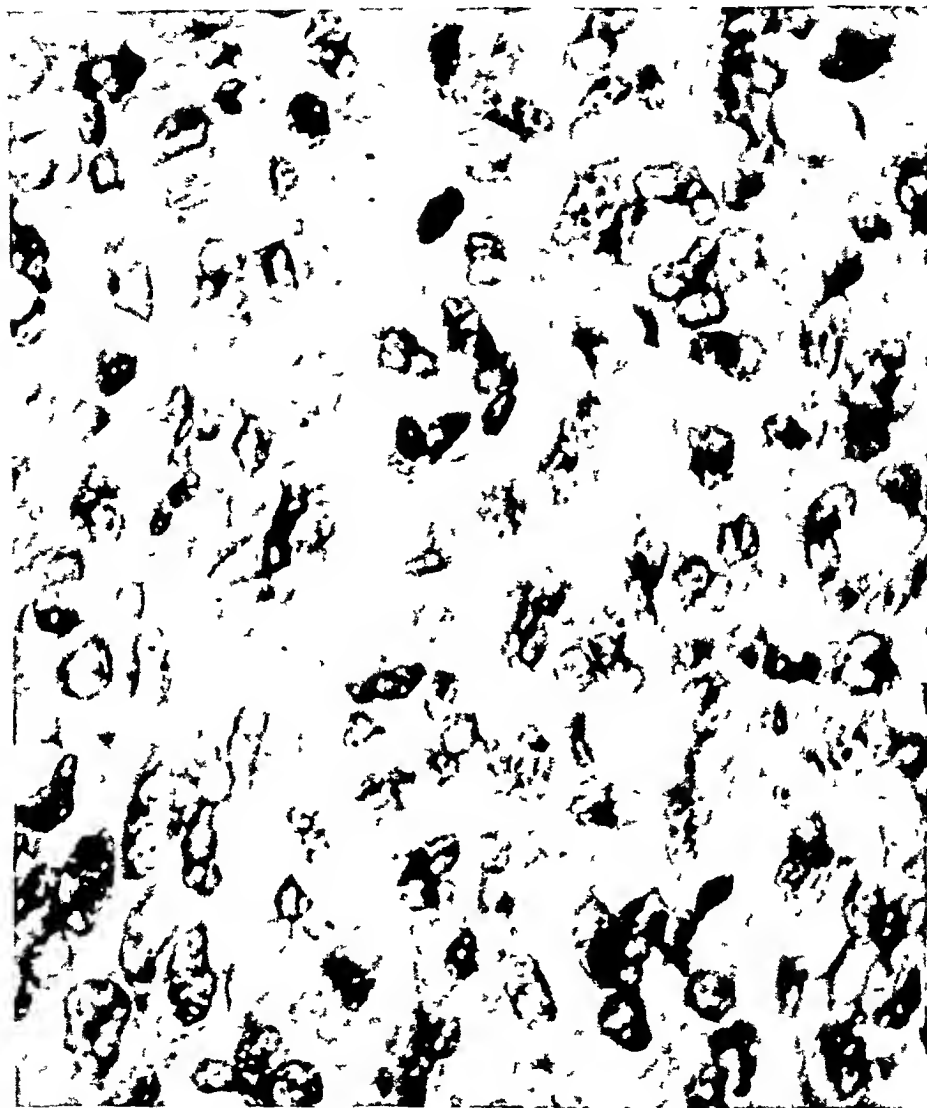


Fig 3—The lobule under high power, showing the ambiguous cellular structure, and the difficulty of differentiating between the growing capillary endothelial cells and the crowded and inactive epithelium

It might not be amiss to suppose that, after birth, this undeveloped gland unable to secrete saliva responded to the secretory stimulations through distention and, perhaps extension of its vessels, so that the whole diseased parotid gland rapidly enlarged

Diagnosis—Congenital capillary hemangioma of the parotid gland

Reported Cases of Angioma of the Parotid Gland and Adjacent Structures

Capillary Angiomas of the Parotid Glands

No	Reporter and Reference	Sex	Age of Patient at First Observation	Age of Patient at Subsequent Observation	Side	Treatment	Result	Size Comment
1	Floss Jährb f Kinderh 19 345, 1882-1883	F	1 months	9 months	R	Operation	Death	Size of large nut
2	Hartman (case 1) Rev de chir 9 736, 1889	F	6 weeks	5 months	F	Excision	Recovery	5 by 4 cm
3	Hartman (case 2) Ibid	F	6 weeks	5 months	F	Excision	Recovery	No change in the skin
4	Hutman (Glenon) (case 3) Ibid	I	At birth	3 years	R	Autopsy	Autopsy	Size of fist and limited to parotid gland
5	Hartman (Berard) (case 4) Ibid	I	1 months	9 months	F	Operation	Recovery	Secured to be hypertrophied parotid gland
6	Hartman (Duke) (case 5) Ibid	I	1 months	9 months	F	Operation	Recovery	At first thought to be an incystic gland
7	von Mangoldt (case 1) Jahrb f Nat u Heilk 6 270, 1897	M	1 months	1 months	R	Excision	Recovery	looked like hypertrophied parotid gland
8	von Mangoldt (case 2) Ibid	I	At birth	1 months	F	Excision	Recovery	Size of fist bluish skin
9	Budone Arch di ostop 14 398, 1907	F	2 months	15 months	R	Excision	Recovery	Size of pigeon's egg
10	Kaufmann, reported by Usui (Arch f klin Chir 16 672, 1881)	M	6 months	3 years	R	Excision	Recovery	Size of pigeon's egg
11	Hartman Bull et mem Soc anat de Paris 79 714, 1901	I	1 month	3 months	R	Excision	Recovery	Little nevus on top of bluish tumor
12	Grulee Surg Gynec Obst 2 71, 1906	F	1 month	11 months	R	Excision	Recovery	Two small new skin bluish over deep tumor
13	Clogg (?) Report of the Society for the Study of Diseases of Children, 1906, vol 6, p 230	I	1 months	7 months	R	Operation	Recovery	thought to be a vascular structure
14	Bragi Arch di ostop 24 237, 1907	I	1 month	2 months	R	Excision	Recovery	Size of hen's egg
15	Hersheimer Centalbl f allg Path u path Anat 19 709, 1908	M	2 months	18 months	R	Excision	Recovery	Size of child's fist
16	Hersheimer Ibid	M	2 months	18 months	R	Excision	Recovery	Plum sized
17	Levitt Berl klin Wchnsch 15 28, 1908	M	2 months	18 months	R	Excision	Recovery	Plum sized
18	Levitt Ibid	M	2 months	18 months	R	Excision	Recovery	Plum sized
19	Hagendorn, mentioned by Usui (Vrach, 1908, no 29), who examined the section, but did not include the case	I	2 months	18 months	R	Excision	Recovery	Plum sized
20	Itinann Inaugural Dissertation Munchen, 1909	F	2 months	18 months	R	Excision	Recovery	Plum sized
21	Rossi Riv di clin pediat 24 1007, 1909	I	1 month	7 months	R	Excision	Recovery	Plum sized
22	Sungorog Chir 17 1333, 1909	I	At birth	8 weeks	R	Excision	Recovery	Plum sized
23	von Haberer Arch f klin Chir 93 817, 1910	I	At birth	8 weeks	R	Excision	Recovery	Plum sized
24	Harras and Suchner Deutsche med Wchnsch 17 190, 1911	M	At birth	8 weeks	R	Excision	Recovery	Plum sized
25	Usui Arch f klin Chir 94 1083, 1911	I	1 month	8 months	R	Excision	Recovery	Plum sized
26	Usui Ibid	I	1 month	8 months	R	Excision	Recovery	Plum sized
27	Gellé and Petit Dufaille Bull et mem Soc anat de Paris 88 185, 1913	M	At birth	10 months	R	Excision	Recovery	Plum sized
28	Triney Riv di clin pediat 13 511, 1915	I	3 months	11 months	R	Excision	Recovery	Plum sized
29	Triney Ibid	I	3 months	11 months	R	Excision	Recovery	Plum sized
30	Triney Ibid	I	3 months	11 months	R	Excision	Recovery	Plum sized

Ref	Author	Sex	Age	Location	Red dot at birth	Time	Excision	Recovery	Size of pigeons (cm)
1	Thomson	M	11 months	At birth	11 months	Excision	Recovery	Recovery	6 by 6 by 1 cm
2	Thomson	M	11 months	At birth	11 months	Excision	Recovery	Recovery	6 by 6 by 1 cm
3	Thomson	M	11 months	At birth	11 months	Excision	Recovery	Recovery	6 by 6 by 1 cm
Subcutaneous Glands									
1	Kerns	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Size of orange
2	Rockel	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Size of orange
3	Wagner	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Size of orange
Carcinomas of the Parotid Gland									
1	Pelzer	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Called a cystic tumor
2	Nott	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Angioma of skin including parotid gland
3	von Margoldt	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Skin angioma everted, parotid paquehm
4	von Margoldt	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Carcinoma angioma of skin and parotid
5	von Margoldt	M	11 months	At birth	11 months	Excision	Recovery	Recovery	The whole parotid region was pusillile
6	Conforti	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
7	Routier	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
Angiomas in the Parotid Region that May or May not Have Affected the Gland									
1	Duke	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Thought to be an aneurysm but a hypertrophied parotid gland
2	Rockel	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Large angioma of neck
3	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Had multiple angiomas
4	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Size of large nut
5	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	No further details
6	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	No details
7	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Caused deformity of angle of jaw
8	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
9	Guellot	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
Angiomas of the Skin of the Parotid Region not Known to Have Affected the Gland									
1	Teale	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Parotid gland not definitely involved
2	Teale	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
3	Teale	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
4	Angier	M	11 months	At birth	11 months	Excision	Recovery	Recovery	
Pulsating Ixodid Lesion and Hematoma Following Traumatism									
1	Polvin	M	11 months	At birth	11 months	Excision	Recovery	Recovery	Followed by arm injury

COMMENT

These tumors are benign but if they are neglected, the vessels progressively increase in size, so that surgical removal becomes more difficult, and the operation is apt to be bloody. Removal of the entire affected gland seems to be the operation of election and has been followed by complete recovery (so far as the case reports show) in twenty-two of thirty-three cases. Care must be taken, however, lest the facial nerve be destroyed. Facial palsy has been reported in five cases.

The tumors occur with about equal frequency on the two sides of the face, right twelve, left, thirteen. They are, however, notably more common in girls (fifteen) than in boys (eight). The tumors are usually noticed immediately after birth, though in one reported case the tumor is said not to have been detected until the sixth month. In two of the cases reported with the necessary data, the patient escaped operation until 3 years of age. The youngest patient to be operated on was only 4 weeks old. The average age at which operation was performed was 9 months.

The size of the tumors removed by operation varied from the size of a pigeon's egg to that of a fist. But regardless of size they must have been of much the same general appearance as it is frequently stated that they looked like hypertrophied parotid glands.

The authors of previous contributions on the subject differed among themselves as to the number of reported cases and the particular reported cases they were willing to admit to the first of the following groups. The conclusions reached by me and my classification of the cases are shown in the following tabulation and bibliography.

The literature on angioma of the salivary glands shows such tumors to be rare. A complete survey of the subject has resulted in the collection of reports of only fifty-seven cases roughly divisible as follows:

- 1 *Congenital Capillary Hemangioma of the Salivary Gland*—The cases are all in infants or small children in whom the entire parotid (or submaxillary) gland immediately after birth began to enlarge for no apparent reason, until it attained to many times the normal size. In some cases, there was a small visible angioma in the skin or some purplish discoloration of the skin. In other cases, there was no gross indication of the nature of the lesion. Of such cases, including the one reported in this contribution, thirty-three are recorded as affecting the parotid gland, and three as affecting the submaxillary gland.

- 2 *Cavernous Angioma of the Salivary Gland*—This group includes seven cases in which a distinct superficial vascular nevus of the skin descended to and invaded the parotid, and nine cases in which a large, widely distributed hemangioma of the side of the face and neck invaded the parotid gland, as well as other adjacent structures.

3 *Vascular Nevus*—These are hemangiomas of the skin over the parotid region which are not known to have invaded or transgressed on the parotid or submaxillary glands. Four cases are recorded.

4 *Pulsating Vascular Lesion*—One such hematoma following traumatism is on record.

SUMMARY

A case of congenital capillary hemangioma of the parotid gland of an infant is described. Reports of thirty-three similar cases have been collected from the literature. The surgical removal of the entire affected gland is the operation of election and results in complete cure in most cases, though facial palsy has occurred in five cases. The tumor is benign. No case of recurrence is on record.

Other varieties of angiomatous disease of the parotid gland are introduced into the bibliographic tabulation for purposes of comparison.

THE EFFECT OF HEMOLYTIC TOXINS ON NERVOUS TISSUE*

ARTHUR WEIL, MD
CHICAGO

In a study of the effect of anemia on the spinal cord based on clinical and microscopic material it had been concluded that anemia in itself does not produce the picture of subacute combined degeneration. It was only in the pernicious type of anemia that this degeneration of myelin sheath and axon was seen. Support was given to the theories of other investigators that one and the same toxin acted destructively on the hematopoietic system and the spinal cord, though the diseases might reveal themselves at different periods.¹

As a result of this histologic research, the idea was conceived to investigate the effect of hemolytic agents on the myelin sheaths of nerve fibers of the spinal cord and peripheral nerves.

Frequently, the attempt has been made to produce degenerative processes of the central nervous system in animals by the injection of hemolytic agents. Experiments with the group of substances producing methemoglobin have been a complete failure. In experiments with the second group of hemolytic substances which act on the stroma or (hypothetical) pellicle of the red blood cells the immense toxicity of these substances had been an obstacle to investigation. It was only recently that Rezek and Kollet² reported on a series of injections of saponin into a group of sixty rabbits only two of which showed paralysis clinically. In the one case that was examined post mortem degeneration of ganglion cells and demyelination of nerve fibers were seen. But the authors did not conclude that this was the direct effect of saponin, they thought rather that the hypercholesteremia or the severe damage of the liver might have been responsible indirectly for the disease of the nervous system.

Attempts to produce demyelination in the living animal by long extended ether or chloroform anesthesia did not meet with success. In test tube experiments, it is possible to dissolve the myelin sheaths with lipid solvents. After treatment with absolute alcohol for twenty-

* Submitted for publication, Nov. 29, 1929.

From the Institute of Neurology, Northwestern University.

1. Weil, A., and Davison, Charles. Changes in the Spinal Cord in Anemia. A Clinicomicroscopic Study, *Arch. Neurol. & Psychiat.* **22**: 966, 1929.

2. Rezek, P., and Kollet, V. Virchows *Arch. f. path. Anat.* **270**: 706, 1929.

3. Weil, A. *Arch. f. d. ges. Physiol.* **223**: 351, 1929.

four hours at 37 C, the myelin sheaths of spinal cords were partly dissolved, indistinct in their outlines. The axons in sections stained with Weil's method were unstained, glia fibers, distinctly stained. After treatment with pyridine for twenty-four hours at 37 C, the myelin sheaths of spinal cords were completely dissolved, the axons of the myelinated fibers stained dark black. It was not possible to obtain demyelination with these solvents in formaldehyde-fixed tissue.

The plan of the present investigation was to study the effect of hemolytic toxins on nervous tissue in test tube experiments. This effect was to be compared with the effect of the same toxin on red blood cells, and the question was to be answered whether the basic principles governing hemolysis by those toxins could also be applied to myelolysis.

METHOD

Representatives of four different groups of hemolytic toxins were chosen for the present investigation: (1) saponin (Merck's purified bark of *Quillaja saponaria*), (2) cobra venom (dried saliva of *Naja nigricollis*, through the courtesy of Dr. T. Friedman), (3) sodium taurocholate (Merck's, about 42 per cent), and (4) streptolysin (strain of *Streptococcus haemolyticus*, through the courtesy of the Department of Bacteriology of Northwestern University, eighteen-hour meat-broth-serum cultures, centrifugated). In addition in control experiments, different substances that form methemoglobin in the animal body were tested together with the influence of different buffer solutions.

Cats and dogs were anesthetized with ether, killed by bleeding and the lower third of the cervical spinal cord or the sciatic nerves were removed under aseptic precautions. The spinal cord was cut into small segments of approximately 0.2 Gm each, which were placed on a layer of cotton in sterilized test tubes. The solution of the substance to be investigated was added and the tube closed by cotton and placed in the incubator. At the end of the experiment the solution was replaced by a diluted solution of formaldehyde U. S. P. (1:5), and the tissue was fixed for three days. It was then embedded in paraffin or a collodion preparation, and sections were stained by Weil's method for myelin sheaths or by a modified light-green fuchsin method. In some experiments, the whole formaldehyde-fixed tissue was impregnated according to the Bielschowsky method.

OBSERVATIONS

The Effect of Hemolytic Toxins on the Myelin Sheaths—The four hemolytic toxins that were investigated produced hemolysis by dissolving the lipid pellicles of the red blood cells.⁴ In a similar way, they dissolved the myelin sheaths of myelinated nerve fibers. That saponin acted on the stroma (pellicle) of the red blood cells and not on the hemoglobin or the hypothetical hemoglobin-lipoid compound, as sug-

⁴ Landsteiner, K. in Oppenheimer, C. *Handbuch der Biochemie*, Jena, A. Kanitz, 1910, vol. 2, p. 459. Blumenthal, G. *Ibid.*, 1925, vol. 3, p. 568. Von Bergmann, G. and Staehelin, R. *Handbuch der inneren Medizin*, Berlin, E. St. Faust, 1927, vol. 4, pt. 2, p. 1745.

gested by Lepeschkin⁵ was demonstrated by experiment as follows. Red blood cells were hemolyzed with distilled water, centrifugated, washed and again centrifugated. The remaining stromata were spread on a glass slide and stained with one of the methods for myelin sheaths (Spielmeyer, Loyez, Weil). They assumed a black color similar to that of myelin sheaths. Another smear with stromata was left for ten minutes at 37 C. in a 1 per cent solution of saponin. After the staining only a pale gray color remained.

One per cent solutions of saponin, cobra venom and sodium taurocholate (2.4 per cent solution of Merck's 42 per cent preparation), as well as eighteen-hour cultures of *Streptococcus haemolyticus* kept twenty-four hours at 37 C., produced a definite demyelination. In transverse sections of spinal cords or sciatic nerves stained for myelin sheaths, a pale, unstained zone could be seen encircling the spinal cord or forming the outer zone of the transversely cut nerve trunks. If solutions of 1 per cent or stronger of saponin were applied for twenty hours under the microscope a loose meshwork of faintly stained axons and glia fibers was seen, intermingled with the fibers of the connective tissue frame work (fig 1, A, B, C and D). The glia nuclei were well stained. In the transitional zone toward the nonaffected tissue, single myelin sheaths were left partly interrupted and thinned out (fig 2, B and D). There was a definite difference in comparison with the controls kept in 0.9 per cent sodium chloride solution, Fleisch's solution or Ringer's solution. The myelin sheaths here were swollen and distorted, but they had not lost their staining qualities and there was never a zone of demyelination as regular in outline as in the first group of experiments (fig 2, A and C). In the controls, the axons, too, were swollen, though stainable with Bielschowsky's method. In the experiments with the hemolytic toxins, the axons appeared to be thinner and more lightly stained than in normal material or in the controls. The astrocytes and their fibers were well stained in Cajal's gold-mercuric chloride preparations of spinal cords. The zone of demyelination could be extended at will into the spinal cord or into the peripheral nerves by artificial lesions or longitudinal sectioning.

The Quantitative Effect of Hemolytic Toxins on the Myelin Sheaths—The amount of red blood cells dissolved by saponin was not proportional to the amount of saponin used but increased disproportionately with rising concentrations. The same condition applied to the dissolution of the myelin sheath. The effect of a 2 per cent solution of saponin seemed to be more intensive than twice the effect of a 1 per cent solution. Under the microscope the destruction of nervous tissue seemed to be more intensive after the use of a 2 per cent solution.

⁵ Lepeschkin, W. W. Abstracts of communications to the XIIIth Internat. Physiol. Congress, Boston, 1929.

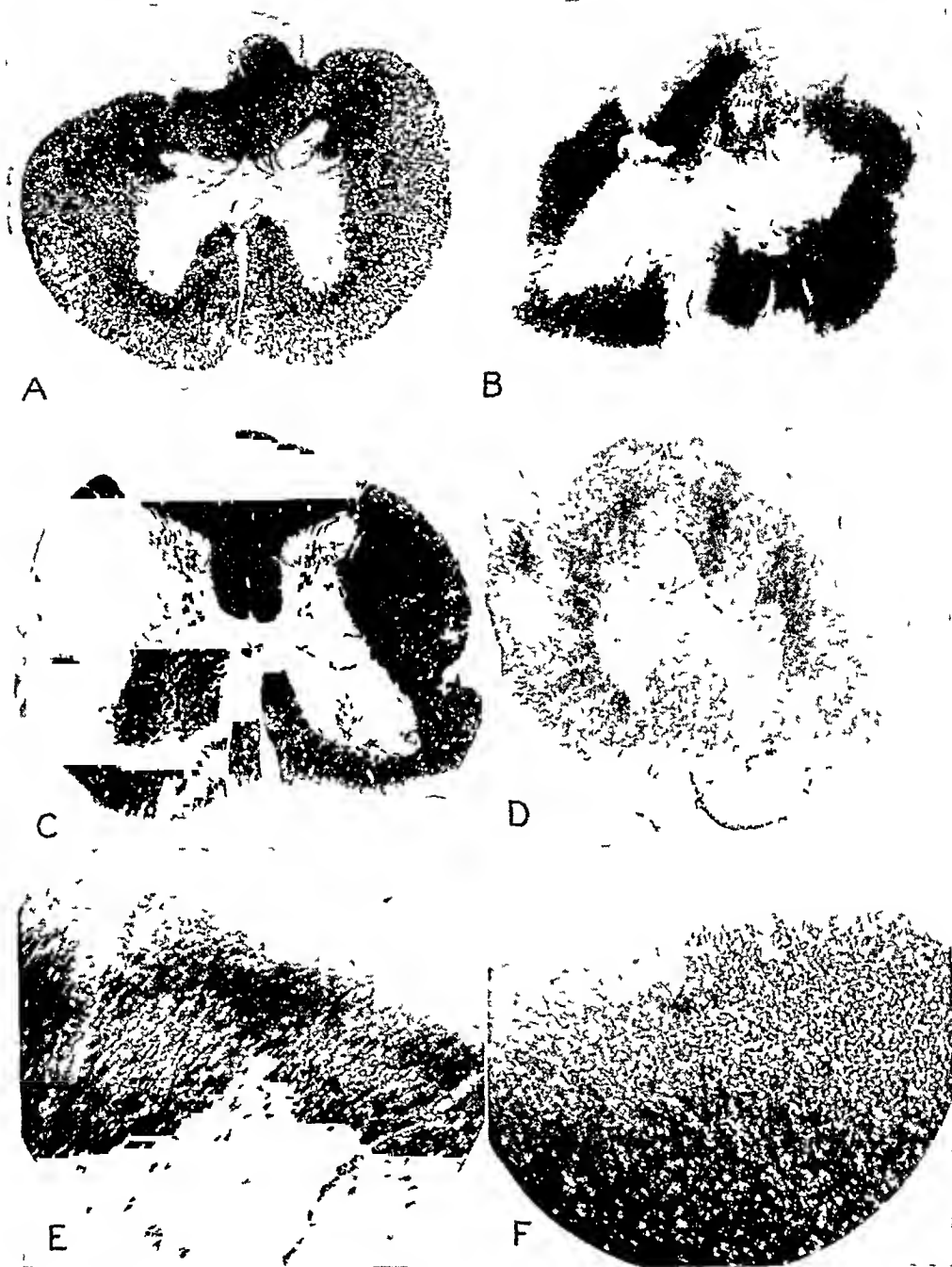


Fig 1—*A*, spinal cord of cat after incubation with 2 per cent saponin in Fleisch's solution, forty-eight hours at 37 C. A transverse section of spinal cord is shown, stained by Weil's method, and seen by Leitz objective 32, ocular 3 X. The purpose is to demonstrate the peripheral zone of demyelination. *B*, spinal cord of dog after incubation with a 1 per cent solution of sodium taurocholate in 0.9 per cent NaCl twenty-four hours at 37 C. The technic of staining in *B*, *C* and *D* is the same as in *A*. *C*, spinal cord of dog after incubation with a 0.5 per cent solution of cobra venom in 0.9 per cent NaCl twenty-four hours at 37 C. Note the demyelination of the posterior roots. *D*, spinal cord of cat after incubation for twenty-four hours at 37 C with 50 cc of meat-broth-serum culture of *Streptococcus haemolyticus* eighteen hours old. *E*, spinal cord of dog (0.150 Gm) in an emulsion of 0.6 Gm of saponin-lectithin 1:5 in 10 cc 0.9 per cent NaCl. A transverse section is shown, stained by Weil's method and seen by Leitz objective 32, ocular 6 X. The purpose is to demonstrate the diminished demyelination as compared with the action of saponin-lectithin 1:1 in *F*. *F*, spinal cord of dog (0.145 Gm) in an emulsion of 0.2 Gm of saponin-lectithin 1:1 in 10 cc of 0.9 per cent sodium chloride. The technic and the enlargement are the same as in *E*. The purpose is to demonstrate the marginal zone of demyelination.

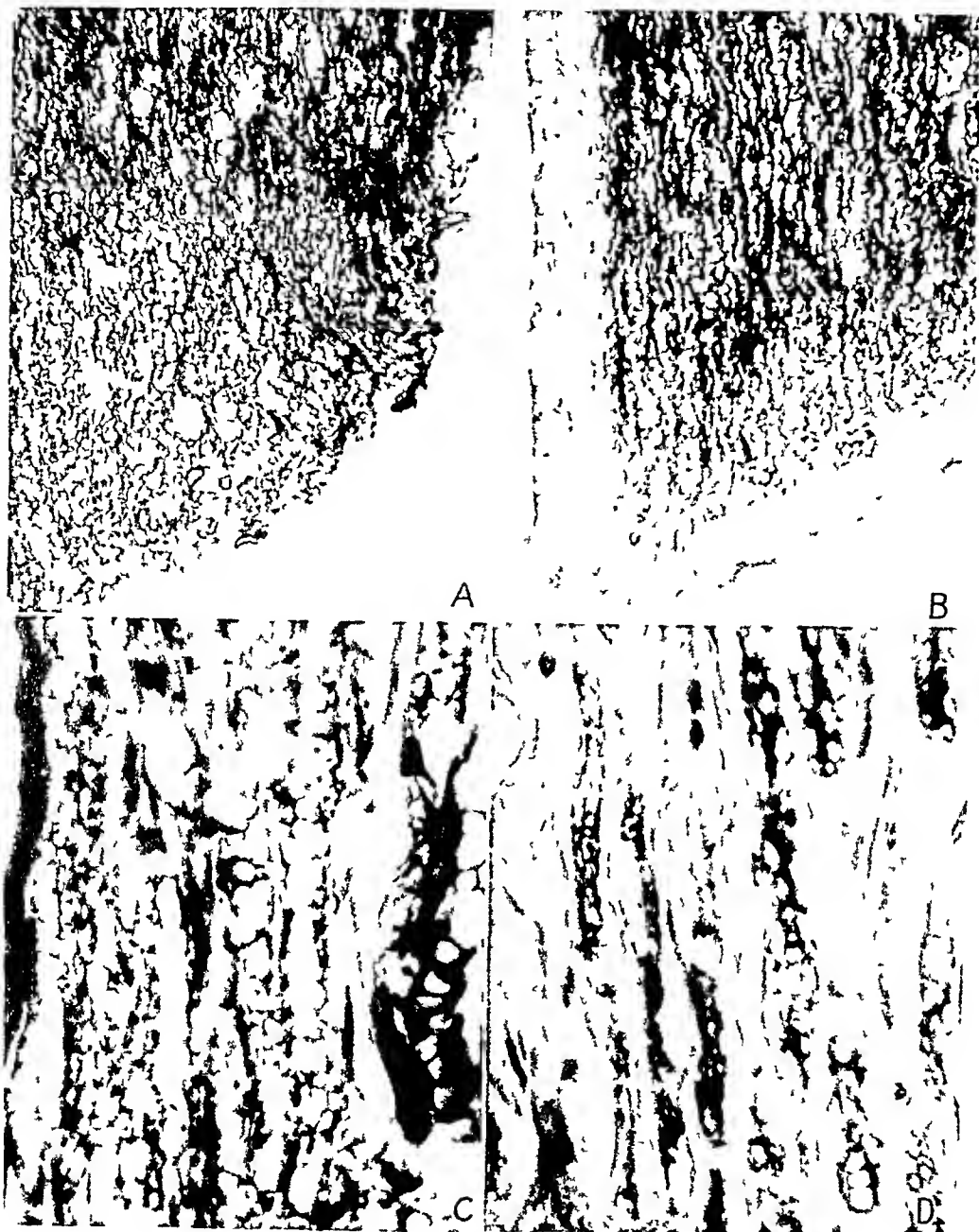


Fig 2—*A* spinal cord of cat in Fleisch's solution seventy-two hours at 37 C. Longitudinal section is shown stained by Weil's method and seen by Litz objective 10 ocular 8 \times . *A* control to demonstrate that seventy-two hours of autolysis did not change the staining qualities and did not produce the marginal zone of demyelination. *B* spinal cord of cat after incubation with 0.5 per cent saponin in Fleisch's solution for twenty-four hours at 37 C. A longitudinal section is shown, stained by Weil's method. The enlargement is the same as in *A*. The purpose is to demonstrate the marginal zone of demyelination at the outer wall and at the cut surface. *C* sciatic nerve of dog in 0.9 per cent solution of NaCl for twenty-four hours at 37 C. A longitudinal section is shown, stained with light green-fuchsin and seen with Litz objective 2 mm, ocular 6 \times . The purpose is to demonstrate the absence of myelin sheath dissolution in the controls. *D* sciatic nerve of dog in 1 per cent solution of saponin in 0.9 per cent NaCl for twenty-four hours at 37 C. A longitudinal section is shown, stained and enlarged as in *C*. The purpose is to demonstrate the dissolution of myelin sheaths.

though the zone of demyelination was not exactly twice as wide as after the application of a 1 per cent solution

In order to determine objectively the amount of saponin which was bound by spinal cords, solutions of the toxin were tested for their hemolytic power at the beginning and the end of the experiment. After incubation at 37 C for forty-eight hours, 1 cc of the solution was diluted with 9 cc of 0.9 per cent sodium chloride, 1 cc of this dilution was added to 1 cc of a 2.5 per cent emulsion of red blood cells which

TABLE 1—*Comparison of Action of Saponin Against Spinal Cords of Cats and Dogs After Forty-Eight Hours' Incubation*

Animal	Mg Saponin per 1 Gm Spinal Cord	Mg Saponin in 1% Solution	1 Cc 0.1% Dilution Equivalent to 0.1% Saponin, Cc	Saponin Absorbed, Mg	Mg Saponin per 1 Gm Spinal Cord	Final Concentration, %
Cat	215	75	0.40	45	200	0.40
Cat	220	100	0.30	70	135	0.30
Dog	210	75	0.43	43	205	0.43
Dog	510	100	0.21	70	158	0.21
Control		50	1.00			1.00

TABLE 2—*Results of Experiments with a 1 per Cent Solution of Saponin and Dog Spinal Cord, Incubated Forty-Eight Hours at 37 C*

Mg Saponin per 1 Gm of Spinal Cord	Absorbed Mg Saponin per 1 Gm Spinal Cord	Final Concentration of Saponin, %	Constant of Arrhenius' Formula*
64	63	0.01	1,377
81	78	0.03	809
100	95	0.06	620
115	114	0.05	840
134	116	0.13	901
200	158	0.21	447
245	177	0.28	414
300	200	0.29	489
348	203	0.40	386
440	240	0.45	469
222	201	0.21	569} spinal cord
315	240	0.30	536} emulsions

* For explanation see under "The Physicochemical Nature of the Process of Demyelination."

had been washed with salt solution. The time for complete hemolysis was determined. At the same time, varying amounts of a 0.1 per cent solution of saponin filled up to 1 cc with 0.9 per cent sodium chloride were added to 1 cc of the blood emulsion, and the time for complete hemolysis was determined.

To give an example of these experiments a protocol is shown in table 1. It illustrates an experiment which was to answer the question whether spinal cords of cats and dogs acted quantitatively differently against saponin.

Table 2 gives the results of experiments carried out in order to determine the amount of saponin which was bound by 1 Gm of spinal cord in solutions of different concentrations.

Most of these experiments were carried out with sections of spinal cords in which the possible retarding influence of the diffusion of the solution into the tissue had been balanced by extending the time to forty-eight hours. The inhibiting influence of saponin on autolysis and fermentative processes makes such an extension possible. When an emulsion of spinal cord was used prepared by grinding the tissue with the solution in a mortar, approximately 20 per cent more saponin was bound than by the intact tissue.

Influence of Time, Minimal Concentration—Twenty-five hundredths of a milligram of saponin in 0.1 per cent solution completely hemolysed 1 cc. of a 2.5 per cent emulsion of blood cells if kept for several hours in the incubator at 37 C., 0.15 mg. of saponin can no longer produce complete hemolysis under the same conditions. In similar investigations of saponin myelolysis, the first effect of a 1 per cent solution could be detected under the microscope after approximately one hour. The

TABLE 3—*Comparison of Hemolytic, Myelolytic and Toxic Effects*

	Saponin	Cobra Venom	Sodium Taurocholate	Strepto- lysin*
Hemolytic effect	100	70	150	20
Myelolytic effect	100	150	20	200
Toxic effect	100	15,000	0	

* 0.2 Gm. of spinal cord of dog in 50 cc. of an eighteen hour culture

maximal effect, measured by the width of the zone of demyelination was practically obtained after twenty hours. A 0.5 per cent solution produced only a minimal effect, a 0.2 per cent solution was ineffective after twenty-four hours' incubation. Controls with serum of dogs and cats, plasma of the same animals and of rabbits, meat-broth, meat-broth-serum, saliva, phenylhydrazine, acetanilid, potassium chlorate and oil of sesame did not show demyelination.

Comparison of the Hemolytic, the Myelolytic and the Toxic Effects—The comparative hemolytic effects of the different toxins were determined by investigating the amount of saponin which was necessary to produce complete hemolysis of 1 cc. of an emulsion of red blood cells within the same time as a given amount of each of the other three toxins in equal dilutions. The myelolytic effects were compared by measuring with an ocular micrometer at an enlargement of 600 times the average width of the zone of demyelination in microns in transverse sections of spinal cords. Approximately the same amount of spinal cord and the same dilution of toxin were used in all experiments of this series. The effect of a 0.1 per cent solution of saponin was taken as a unit in testing the hemolytic effect and that of a 1 per cent

solution of saponin was used as a standard in comparing the myelolytic effects. The toxic effects were determined arbitrarily by comparing the lengths of time that it took the various toxins to kill white rats of similar weight after intra-abdominal injection, the same amount of toxin being used in each instance.

The Neutralizing Effect of Lipoids on the Hemolytic, Myelolytic and Toxic Action of Saponin—It has long been known that cholesterol and lecithin added to saponin reduce its hemolytic power. The same is true for a combination of lecithin and streptococcus hemolysin (Gordon and Stansfield⁶). Small amounts of lecithin added to saponin do not have this effect, while large amounts inhibit hemolysis (Kobert⁷). In order to find out whether the myelolytic and toxic effects of saponin

TABLE 4—*The Toxicity of Different Saponin-Lipid Combinations as Indicated by the Time Each Took to Kill After Intra-Abdominal Injection*

Combination Injected	Rat Weight, Gm	Mg Substance	Mg Saponin per 100 Gm Weight	Minutes Before Death	Evaluation of Toxic Effect
Saponin	183	36	20	123	100
Saponin lecithin 1:1	174	70	20	172	72
Saponin lecithin 1:5	168	205	20	253	49
Saponin	123	37	30	112	100
Saponin lecithin 1:1	120	72	30	106	105
Saponin lecithin 1:5	120	220	30	227	47
Saponin	115	29	20	132	100
Saponin galactolipids 1:1	130	52	20	109	121
Saponin galactolipids 1:5	130	155	20	208	64
Saponin	146	44	30	122	100
Saponin galactolipids 1:1	129	78	30	119	102
Saponin galactolipids 1:5	142	255	30	122	100

are influenced in the same way by combinations with lipoids, as is the hemolytic effect, experiments were carried out as follows:

Following Kobert's example, recrystallized cholesterol and different raw lipids, as well as purified lecithin, obtained with MacLean's method from dogs' brains and spinal cords, were added to saponin, and the mixtures were boiled with absolute alcohol (100 parts) in the reflux condenser for thirty minutes. The alcohol was evaporated, and the remaining substance was taken up with chloroform. It was found that the mixture of saponin with lecithin, cephalin or galactolipids completely changed its physical properties. The remaining mixtures were easily soluble in chloroform and gave emulsions with water. The combinations with cholesterol and sphingomyelin were not as successful. After treatment with chloroform, approximately 75 per cent of the original saponin remained insoluble. Further experiments are necessary to prove whether an extended time of boiling gives better results. The different combinations which were obtained were tested for hemolysis, myelolysis and toxicity in the same way as was described for the four toxins in the preceding paragraph (fig 1, *E* and *F*).

⁶ Gordon, J., and Stansfield, F. R. *Brit J Exper Path* **10** 191, 1929.

⁷ Kobert, R. *Beitraege zur Kenntnis der Saponinsubstanzen*, Stuttgart Ferdinand Enke, 1904.

In order to give an illustration of the toxic effect of saponin and its different lipid combinations, some protocols are copied in table 4. Two different combinations with lecithin and galactolipids were tested, one in which one part of saponin had been combined with one part of the lipid and a second in which one part of saponin had been combined with five parts of the lipid. In table 5 the experiments with 30 mg saponin per hundred grams of weight are selected for comparative purposes.

The inhibitory effect of lecithin on sodium taurocholate was much more pronounced. Five parts of egg-lecithin completely neutralized the toxic and myelolytic effect of one part of the toxin.

The Neutralizing Action of Brain Emulsion and Red Blood Cells on the Hemolytic, Myelolytic and Toxic Effects of Saponin—The experiments of Flexner and Noguchi⁸ demonstrated that brain emulsion added to cobra venom reduces its toxic effect while red blood cells added to the toxin do not influence its toxicity. Similar experiments were

TABLE 5—*Comparison of the Hemolytic, Myelolytic and Toxic Effects of Saponin-Lipid Combinations*

	Saponin	Saponin Lecithin 1:1	Saponin Lecithin 1:5	Saponin Galacto- lipids 1:1	Saponin Galacto- lipids 1:5
Hemolytic effect	100	100	Trace	100	Trace
Myelolytic effect	100	110	31	100	100
Toxic effect	100	105	47	102	100

carried out with saponin. Dogs erythrocytes to the amount of 7.5 cc, washed twice with 0.9 per cent sodium chloride solution were mixed with 1.5 cc of a 2 per cent solution of saponin. The mixture was incubated for two hours at 37 C and then centrifugated. A residue of intact red blood cells remained. The supernatant fluid added to a fresh blood cell emulsion (0.5 cc to 1 cc of a 2.5 per cent blood emulsion with 0.5 cc of 0.9 per cent sodium chloride) did not produce hemolysis within two hours while 1 cc of a 0.1 per cent solution of saponin produced complete hemolysis immediately.

The mixture of red blood cells and saponin (7.25 cc) was injected intra-abdominally into a white rat of 100 Gm weight, which died after 273 minutes. The injection of a corresponding amount of saponin in 2 per cent solution (1.5 cc) into the control, i.e., 30 mg of saponin per hundred grams of weight, killed the control after 102 minutes.

Two grams of gray matter and 2 Gm of white matter from a dog's brain were each emulsified with 3 cc of a 2 per cent solution of saponin, and the mixtures were incubated for two hours at 37 C. Hemolysis could no longer be produced by the mixture of saponin and white matter with ten times the amount of the minimal hemolytic dose.

⁸ Flexner, S., and Noguchi, H. J. Exper. Med. 6: 279, 1902.

of saponin. The mixture of saponin and gray matter had not completely lost its hemolytic effect although, expressed in saponin units it was only $\frac{1}{10}$. These mixtures injected into white rats in amounts corresponding to 30 mg. of saponin per hundred grams of weight were much less toxic than saponin. After six hours, both the animal into which the emulsion of gray matter and saponin had been injected and that into which the emulsion of white matter and saponin had been injected were still alive.

In another series of experiments the whole brain substance was emulsified with saponin. After two hours' incubation at 37 C., the mixture was centrifugated, and the supernatant fluid was injected into rats. As in the preceding experiments, the animals were still alive after six hours, while the controls, into which saponin only had been injected, died within two hours. The demyelination of spinal cords in test tube experiments was influenced in the same way as the toxic effect. The spinal cord which had been incubated with the mixture of saponin and red blood cells showed only a small peripheral zone of demyelination with greater damage to the posterior roots. The spinal cord which had been incubated with the supernatant fluid of the centrifugated mixture of saponin and brain substance, presented only a trace of demyelination in the outer zone. A similar protecting influence against the action of saponin was noticed in controls in which spinal cord was incubated with mixtures of saponin and dog serum.

The Physicochemical Nature of the Process of Demyelination — The question arises as to whether the dissolution of the myelin sheaths by the hemolytic toxins which were investigated follows the same physicochemical laws that govern the hemolysis of red blood cells. In studying sections of spinal cords and nerves that have been under the influence of saponin, one is under the impression that the sheaths are dissolved or melted away as a structure of ice melts when heated. The longitudinal sections in figure 2 *B* and *D* represent this thinning out and gradual disappearance of the myelin sheaths in the transitional zones. Spinal cords treated with sodium taurocholate differ histologically somewhat from those treated with the three other toxins. One sees numerous black globules in sections stained by Weil's method. The globules in the outer zones are smaller and less numerous than those in the transitional zone.

The hemolytic action of these toxins has been generally ascribed to the dissolution or destruction of the lipoids of the stroma (pellicle) of the red blood cells. It was assumed either that the toxin combines directly with the lipoids as in the case of saponin (Kobert), or that, as in the instance of cobra venom in lipids (lecithin and cephalin) the radical of the unsaturated fatty acid was split off and the remaining

rest (lysolecithin and lysocephalin) acted as a toxin (Kyes, Lueddecke, Delezenne and Ledebt Levene and Rolf and others⁹)

The effect of saponin on the lipids of the spinal cord can be controlled by analyses for phosphorus. If one carries out a fractional extraction of spinal cord by MacLean's method, one finds that after treatment with solutions of saponin approximately 25 per cent of the total phosphorus has been transferred into the solution. In experiments with brain substance, this amount is approximately 47 per cent. Although saponin applied in concentrated solutions (3 per cent) inhibits autolysis, it is not possible to decide whether or not the increase of phosphorus in water soluble form is due only to the emulsifying effect of the saponin. Experiments with nervous tissue in which fermentative processes have been inhibited by heating or otherwise may give a better answer to this question.

TABLE 6—*Distribution of Phosphorus After Fractional Extraction of Nervous Tissues*

	Percentage of Total Phosphorus					
	Brain			Spinal Cord		
	Normal	Saponin*	Autolysis†	Normal	Saponin*	Autolysis†
Water solution		47.0	76.0		25.0	62.6
Acetone extract	16.3	9.7	9.5	7.3	17.6	15.0
Alcohol extract	54.7	31.5	6.7	77.2	47.0	19.0
Residue	29.0	11.8	7.8	15.5	10.4	1.1

* Dogs' brains and spinal cords used with 10 cc. of 5 per cent solution of saponin per 1 Gm. of substance.

† For the experiments with autolysis 10 cc. of 0.9 per cent sodium chloride was used per 1 Gm. of substance. The mixtures were kept for forty-eight hours at 37°C.

Table 6 reports the results of fractional extractions of normal nervous tissue, brain and spinal cord after treatment with saponin and after autolysis.

The amount of red blood cells dissolved by saponin is not proportional to the amount of saponin used, but increases disproportionately with rising concentrations. The same is true for the binding of hemolytic amboceptors and for the binding of saponin to the spinal cord as demonstrated in table 2. Arrhenius¹⁰ believed that the binding of the hemolytic amboceptor to red blood cells could be quantitatively expressed by the formula $B = K C^n$. B is the amount of the absorbed amboceptor, C is the concentration of the system at the end of the experiment, K and n are constants ($n = \frac{2}{3}$ in the experiments of Arrhenius). If one calculates K for the absorption of saponin by spinal cord in table 2, one finds that the values for K are surprisingly constant if one comes to

⁹ Literature in Delezenne, C. and Fourneau, E. *Bull. Soc. chim. biol.* **15** 421, 1914. Levene, P. A. and Rolf, I. P. *J. Biol. Chem.* **55** 743, 1923.

¹⁰ Arrhenius, S. *Immunochemie. Ergebn. d. Physiol.* **7** 480, 1908.

final concentrations which are still strong enough to produce myelolysis, i e., concentrations of more than 0.2 per cent

Arrhenius concluded from his experiments that the distribution of the hemolytic amboceptor between red blood cells and the serum followed the law of distribution of a substance between two solvents. Blumenthal⁴ opposed this view. In quoting the literature on this subject, he summarized the different theories which try to explain the phenomenon of hemolysis. The present tendency seems to be to explain it by comparing the binding of the hemolytic amboceptor to the red blood cells with the adsorption of colloids.

It may be sufficient for the purpose of this paper to point out the constancy of K in the application of Arrhenius' formula to the binding of saponin to spinal cord.

TABLE 7—*Lipoid Content of Red Blood Cells and of Nervous Tissue*

Lipoid	Dog				Cat		
	100 Ce Erythro- cytes*	Brain†		Spinal Cord‡	100 Ce Erythro- cytes*	Brain†	Spinal Cord‡
		Gray Matter	White Matter				
Cholesterol	0.215	2.81	3.94	5.31	0.232	2.48	5.57
Lecithin	0.245	0.87	1.08	2.38	0.310	1.10	2.58
Total lipoids‡	0.562-0.634	10.60	19.60	24.20	0.531-0.589	13.80	23.40

* The figures for cholesterol of red blood cells are from the publications of Knud and Iwatsuru, those for lecithin of red blood cells from Abderhalden (quoted in Oppenheimer, footnote 4, p. 560).

† The figures for nervous tissue were copied from Weil (J. Biol. Chem. 83: 601, 1929). The latter figures are for percentages of fresh tissue.

‡ The total lipoids of the red blood cells were calculated as triolein. The numbers for the total lipoids of the nervous tissues represent the total amount of lipoids after extraction by acetone and following alcohol extraction in the Soxhlet apparatus.

The results of the experiments to combine saponin with varying amounts of lipids demonstrated the ability of the toxin to form emulsions with large amounts of the substance to become emulsified. It could be shown that with increasing amounts of lipids added the hemolytic power, in test tube experiments, became gradually diminished. It seemed that galactolipids did not act in the same direction as lecithin. The combination of saponin-lecithin 1:5 was much less hemolytic, myelolytic and toxic than the combination 1:1. In the combinations with galactolipids, however, it did not make any difference whether one or five parts were added to one part of saponin (tables 4 and 5). It should be noted that myelolytic and toxic effects were affected in the same manner.

In order to obtain a basis for the explanation of the different binding powers of red blood cells and of nervous tissue for saponin by their different lipid contents, the figures in table 7 are cited.

These figures indicate that 1 Gm. of spinal cord contains 242 mg. total lipoids (dog) or 234 mg. (cat), and that 1 cc. of red blood cells

contains 6 mg total lipoids (dog) or 56 mg (cat) The optimal amount of saponin which may be bound by 1 Gm of spinal cord is 240 mg The minimal amount of saponin which is sufficient to produce complete hemolysis of 1 cc of red blood cells is approximately 5 mg (0.25 cc of 0.1 per cent saponin for 1 cc of 5 per cent red blood cells) If one combines these different facts, one finds that in hemolysis, as well as in the process of myelolysis, one part of Meick's saponin is bound by approximately one part of total lipoids

The Identity of Hemolysins, Myelolysins and Neurotoxins—The classic experiments of Ehrlich¹¹ in demonstrating the different action of the hemolytic (tetanolysin) and the toxic (tetanospasmin) principles in the tetanus toxin belong to the fundamentals of the side (lateral)-chain theory If one adds erythrocytes to tetanus toxin, it loses its hemolytic power, in test tube experiments ("the tetanolysin is bound"), while this mixture still produces tetanus after injection into an animal ("the tetanospasmin remains free") A similar experiment to demonstrate the difference between the hemolytic and the neurotoxic principles in cobra venom was carried out by Flexner and Noguchi⁸ Cobra venom mixed with brain emulsion was still hemolytic, but much less toxic, while a mixture of blood cells and venom was very toxic They concluded that their experiments supported the hypothetical considerations of the lateral chain theory of immunity, i.e. that brain cells contain the receptors for the neurotoxic constituent of the venom, while red blood cells furnish the receptors for the hemolytic principle

If one replaces the words "tetanustoxin" and "cobra venom" by the word "saponin," the statement of the results of the experiments would read as follows 1 If one adds erythrocytes to saponin, it loses its hemolytic power, while the mixture still produces death after injection into an animal 2 Saponin mixed with brain emulsion is still hemolytic but less toxic, while a mixture of red blood cells and saponin is very toxic These facts have been fulfilled experimentally, as was demonstrated in the protocols under "Comparison of the Hemolytic, the Myelolytic and the Toxic Effects"

In these experiments and in the experiments with saponin-lipid combinations, the chemically unknown animal and bacterial toxins had been replaced by a chemically relatively well known substance The active principle of Quillaja saponin has been isolated in the form of sapotoxin (Brandl¹²) It is a chemically uniform substance which dissolves red blood cells, which produces local inflammation after subcutaneous injection and which injected in larger amounts produces death One may assume that its action on the myelin sheath is the same as that of saponin,

11 Ehrlich, P Berl klin Wchnschr 35 273, 1898

12 Brandl, J Arch f exper Path u Pharmacol 54 245, 1904

its mother substance. In other words, the hemolytic, myelolytic and toxic principles in saponin are represented by one and the same chemical unit. Furthermore, these different effects on red blood cells and the nervous tissues may be influenced in the same way by lipoids, by red blood cells and by brain emulsions as the hemolytic and toxic effects of bacterial and animal toxins. One is able at will to reduce the hemolytic action without impairing the myelolytic and toxic effect of saponin. Taking all these different facts together, one seems justified in establishing the following hypothesis for further research:

The effects of bacterial and animal toxins which at the same time act in a hemolytic, myelolytic and toxic manner are not reproduced by different principles but by one and the same toxic substance. Its physiologic action is determined by the lipid content of the tissue on which this toxin is acting and by the lipid content of the solvent of the toxin. Combinations of these toxins with the lipoids of red blood cells, in test tube experiments, may be split up again after contact with the living tissues, and the neurotoxic effect may reveal itself, though delayed. Combinations of these toxins with brain emulsions undergo the same action after injection into an animal. In test tube experiments with erythrocytes, their adsorption to the lipoids of the nervous tissues prevents a competitive adsorption to the lipoids of the red blood cells.

The Relation of Myelolysis by Toxins to Neurologic Diseases—The classic examples of primary myelin sheath degeneration in man are multiple sclerosis and subacute combined degeneration in pernicious anemia. It is tempting to try to explain the histologic pictures of demyelination by the action of a toxin which might be related to the group of hemolytic toxins which were investigated. But besides proving that such a toxin is present in these diseases, it has to be demonstrated how such a toxin circulating in the blood and in the lymphatic fluids can penetrate into the central nervous system. That this barrier of blood and cerebrospinal fluid (Blut-Liquorschranke) may be penetrated under certain conditions in disease has been well demonstrated by the investigations of Walter and others.¹³ It is known that hemolysins are found in the cerebrospinal fluid in syphilitic disease (Weil and Kafka).¹⁴ Singer and Muenzer¹⁵ demonstrated hemolytic amboceptors in the spinal fluid of patients suffering from general paresis and chronic epidemic encephalitis six days after the injection of sheep blood intravenously. Histologic pictures of marginal demyelination of the spinal cord resembling the figures that are produced in this paper have been

13 Walter, F. K. Arch. f. Psychiat. **79** 363, 1927. Weil, E. Ztschr. f. d. ges. Neurol. u. Psychiat. **24** 507, 1914.

14 Weil, E., and Kafka, V. Med. Klin. **7** 1314, 1911.

15 Singer, E. and Muenzer, T. Ztschr. f. Immunitätsforsch. u. exper. Therap. **47** 532, 1926.

described by Spitzer¹⁶ as occurring in *tabes dorsalis* and by Martin¹⁷ as occurring in amyotrophic syphilitic meningomyelitis. Of interest in connection with the problems presented is the report of Laignel-Lavastine and Koressios¹⁸ that they succeeded in improving the conditions of patients suffering from multiple sclerosis by the injection of hemolytic rabbit serum (against sheep blood).

CONCLUSIONS

The hemolytic and myelolytic actions of saponin, sodium taurocholate, cobra venom and streptolysin were studied. It could be demonstrated that hemolytic toxins dissolve the myelin sheath of nerve fibers in the same way as they destroy the pellicles of red blood cells.

The relation of the hemolytic effects to the myelolytic effects of the four toxins may vary. Compared with saponin, cobra venom and streptolysin are more myelolytic than hemolytic, in test tube experiments, while the action of sodium taurocholate is similar to that of saponin, though potentially stronger.

The amount of saponin bound by 1 Gm of spinal cord increases with the amount of saponin present. This phenomenon corresponds to the action of hemolytic antibodies on red blood cells. The constants of Arrhenius' formula calculated for the saponin-cord system are relatively constant for final concentrations of more than 0.2 per cent.

The action of different lipids (lecithin, cephalin and galactolipids) on saponin was studied. It could be demonstrated that mixtures of equal parts of saponin and lipids did not reduce the hemolytic, myelolytic and toxic effects. Mixtures of one part saponin with five parts of the lipids were much less hemolytic. But while the combination with lecithin was also reduced in its myelolytic and toxic action, the combination of saponin with five parts of galactolipids had the same myelolytic and toxic effect as the 1:1 combination, if high toxic doses were used. The inhibitory effect of lecithin on sodium taurocholate was much more pronounced than the effect on saponin. Five parts of lecithin added to one part of sodium taurocholate completely inhibited the latter's hemolytic, myelolytic and toxic action.

Mixtures of saponin with red blood cells were no longer hemolytic and less myelolytic and toxic than the corresponding amount of saponin alone. Mixtures of saponin with emulsion of gray matter or emulsion of white matter of brains or emulsion of total brain substance were much less hemolytic and less myelolytic and toxic than saponin.

16 Spitzer, H. *Archiv f. d. neurol. Inst. d. Wien Univ.* **28**: 264, 1926.

17 Martin, J. P. *Braun* **48**: 162, 1925.

18 Laignel-Lavastine, M. and Koressios. *Paris med.* **1**: 190, 1929.

HUMAN INFECTION WITH ACTINOMYCES NECROPHORUS

BACTERIOLOGIC AND PATHOLOGIC REPORT OF TWO CASES
TERMINATING FATALLY *

JOHN SUMTER CUNNINGHAM, M D

ROCHESTER, N Y

Necrobacillosis or infection with *Actinomyces necrophorus*, is relatively common in animals but in man it is exceedingly rare. Descriptions of the disease and its wide occurrence in animals, of the characteristics and biology of *Act. necrophorus*, and of the pathology and bacteriology of the organism as observed in experiments may be found in the more or less exhaustive reports of Jensen¹ (1912), Weinberg and Ginsbourg² (1927) and Albrecht³ (1929).

ANIMAL INFECTIONS

Veterinarians are familiar with the coagulation necroses and gangrene produced by the organism in the various animal tissues. Necrobacillosis has been described as responsible for the following common animal diseases: "calf diphtheria", necrotic stomatitis of calves, lambs and pigs, "foot-rot" of cattle and sheep, gangrenous dermatitis—"grease-heel" and "necrotic quittor"—of horses and mules, the necrotizing ulcerations of the intestines in hog cholera (T. Smith, Bang), and multiple infarction abscesses in the lungs and livers of cattle and swine. The organism may spread by way of the lymphatics and produce metastatic nodular abscesses. Spontaneous necrobacillosis has been observed in more than fifteen animal species. It occurs in wild animals, such as the antelope, deer, kangaroo and ape. Chickens and birds have the disease usually as avian diphtheria. Enzootic infections in guinea-pigs and rabbits have been reported. The disease in horses and mules is moderately fatal and has a high rate of morbidity. Postpartum necrobacillosis of the vagina and uterus of the cow occurring in epidemics

* Submitted for publication, Oct 4, 1929.

* From the Department of Bacteriology, School of Medicine and Dentistry, University of Rochester.

1 Jensen, C. O. Die vom Nekrosebacillus (*Bacillus necroseos*) hervorgerufenen Krankheiten, in Kolle and Wassermann. Handbuch der pathogenen Mikroorganismen 6 234 1913.

2 Weinberg, M., and Ginsbourg, R. Données récentes sur les microbes anaérobies. Monograph de l'Institut Pasteur, no 211, 1927.

3 Albrecht, B. Infektionen durch Nekrosebacillen in Kolle, Kraus and Uhlenhuth. Handbuch der pathogenen Mikroorganismen 6 673, 1929.

and with a high mortality has been reported. Calves born of such animals frequently have so-called navel-ill or omphalophlebitis, with metastases to the liver.

The infection enters the body following injury to the skin or mucous membranes, and may spread by way of lymphatics or the blood stream to any of the body tissues. A similar pathologic process—localization of nests of the organisms, inflammation, formation of an abscess wall, necrosis, gangrene, sloughing, perhaps followed by healing—is observed in simple infections of the skin and mucous membrane. If the infection is not localized, thrombophlebitis results and embolic metastases may occur to the viscera, bones and joints. These metastatic infections are attended by infarction, necrosis and gangrene. Occasionally, proliferative changes occur. The spread through the lymphatics takes place most frequently in the lungs, where “daughter” nodules or abscesses are seen extending radially from a large central abscess. The liver is commonly infected by transmission of the organisms in the portal blood stream from primary infections in the intestines.

The early work of isolating and identifying *Actinomyces necrophorus* and correlating the lesions produced by it attracted the attention of some notable bacteriologists. Robert Koch, Loeffler, Theobald Smith, Bang and many others investigated the organism. Dammann probably first observed the clinical manifestation of *Act. necrophorus* in his investigation of diphtheritic infections in calves in 1876. He thought, however, that the disease was caused by *Bacillus diphtheriae*. Loeffler (1884) disproved this by showing that the predominating organism in the diphtheritic lesions was a gram-negative, thin rod with filamentous forms which he found on the border between the sound and the necrotic tissue. Koch had previously (1881) found an organism of similar morphology in the sweat glands of sheep having “sheeppox.” Shutz (1888) found similar filiform bacilli in the livers of cattle, and succeeded in transferring them into rabbits and mice. Theobald Smith (1889) saw long, gram-negative bacilli in the intestinal lesions of hog cholera. In 1890, Bang identified the organism in hog cholera, and gave it the name “nekrosebazillus.” Schmorl⁴ (1891) isolated and cultured, for the first time, the same organism from necrotic lesions of rabbits during a virulent epizootic. Numerous other workers have subsequently confirmed these results and have investigated the morphologic, cultural and pathologic characteristics of *Act. necrophorus* in animals.

HUMAN INFECTION

Instances of authentic infection with *Act. necrophorus* in man are rare. There are in the literature several presumptive reports of acute

⁴ Schmorl, G. Ueber ein pathogenes Fadenbacterium (*Streptothrix cuniculi*), Deutsche Ztschr. f. Tiermed. **17** 375, 1891.

infection with *Act necrophorus* following exposure to animals with necrobacillosis. These were usually instances in which veterinarians had attacks consisting of chills and fever, malaise, weakness, thirst and dysphagia, and showing a pharyngeal membrane (Dammann, Casper and Schumann). No cultures were taken. Recovery followed. Hutyra-Marek similarly observed linseed-sized nodules on the hands of a shepherd occurring during an enzootic of necrobacillosis in a herd of sheep. The lesions ulcerated in three or four days, and in ten days had healed completely. Ellermann⁵ (1905) more nearly approached a diagnosis of necrobacillosis in reporting the case of a 9-months old infant dying with pseudo-diphtheria, laryngitis and pneumonia. Culture of the necrotic membrane failed to reveal diphtheria bacilli, but sections of the uvula showed long, threadlike, gram-negative bacteria in the caseous tissue nearest the living structures. The strong resemblance of these bacilli to *Act necrophorus* and the similarity of the lesions to those of "calf diphtheria," in the absence of a positive culture for *B diphtheriae*, caused him to suggest this as a case of primary infection with *Act necrophorus*. Reiner Muller found similar organisms in the mucous membrane of a girl with angina.

Apparently, there are on record only three reports of proved infection with *Act necrophorus* in man. The cases were all of infection in the skin. Schmorl⁴ (1891) himself and one of his assistants each had a small abscess on one finger from handling rabbits with spontaneous and experimental necrobacillosis. Stained smears of the pus showed the characteristic gram-negative filiform bacteria originally cultivated and described by him. The lesions were chronic and healed slowly. Steman and Shaw⁶ (1910) and Shaw⁷ (1925) isolated the organism in pure culture from the large necrotic vesicles of a lesion on the hand of a government meat inspector. The patient, while dissecting an ulceration on the lip of a sheep, had accidentally scratched his left hand on one of the sheep's teeth. Following this injury there was local redness, with swelling and severe pain. When the patient was examined by the authors, he had, over the back of the left hand, an extensive area of coagulation necrosis, accompanied by large vesicles. The entire left extremity was swollen to the shoulder. The color of the lesion varied between gray and purple. The lesion measured $2\frac{1}{2}$ by 2 inches (6.27 by 5 cm), with a highest elevation of about $\frac{3}{4}$ inch (1.83 cm), and was grayish-purple. Treatment consisted of free drainage and moist

⁵ Ellermann, V. Einige Falle von bakterieller Nekrose beim Menschen, Centralbl f Bakteriologie, O **38** 383, 1905.

⁶ Steman, C. M., and Shaw, F. W. Necrobacillosis of the Skin, J. Kansas M. Soc. **10** 405, 1910.

⁷ Shaw, F. W. Necrobacillosis. Bull. Medical College of Virginia. March, 1925.

antiseptic packs. The patient had a temperature as high as 39.4 C (102.9 F) for one week, in three weeks, the wound had entirely healed. The third case of human infection is reported by Van Wering⁸ (1923). *Act. necrophorus* was isolated in pure culture from a lesion on the forearm of a man who had been bitten by a cow. He had a temperature ranging between 38 and 39 C (100.4 to 102.2 F), a cluster of small abscesses on the forearm and lymphangitis and axillary lymphadenitis. A bluish discoloration appeared and the lesion became necrotic in the center and possessed a raised rim of indurated granulation tissue. The culture of the organism was obtained from tissue excised from this border area after cauterization. After varied nonsurgical treatment the lesion healed.

Two additional cases of necrobacillosis in man, both terminating fatally, presenting hitherto undescribed clinical and pathologic features of systemic infection in man, and verified by bacteriologic studies, are described in the following paragraphs.

REPORT OF CASES

CASE 1—*History*—B. M., a white girl aged 19, unmarried, a clerk, was admitted to the medical service of the Strong Memorial Hospital at midnight, Dec. 25, 1928, complaining of weakness, malaise and fever. Symptoms were first noticed with the onset of malaise ten days before. Two days later, headache and feverishness were complained of. The following day, seven days before admission, the patient was forced to bed feeling extremely ill. She had in addition to the symptoms previously noted three severe chills in succession and a temperature as high as 103 F (39.4 C) accompanied by sore throat pain throughout the neck, shoulders and back, and inability to retain food or fluids. Photophobia and ocular pruritus were present. These symptoms persisted, with high fever, vomiting and daily chills. On the seventh day, there was a slight remission. On the eighth day the sore throat had disappeared, however, a marked exacerbation of all symptoms occurred, with fever as high as 105 F (40.6 C). On the tenth day (the day of admission), the patient complained of severe pain in the region of the left hip.

The patient's general health had always been good. She had had measles, mumps, varicella and influenza in childhood and swelling of the cervical glands for a few days three months previous to admission. Five months before admission, the patient had been delivered, without complication of a normal full-term child.

Physical Examination—On admission, the patient lay quietly in bed, appearing well-nourished, fairly comfortable, alert and cooperative. The temperature was 40.3 C (104.5 F), the pulse rate was 84, and the respiration rate, 24. The skin was hot and dry without petechiae or eruptions. Breathing was somewhat labored and rapid. The patient had no immediate complaint aside from pain in the left hip on movement of the left thigh. There was moderate enlargement of the cervical group of lymph nodes. The sclerae were subicteric, the eyes were otherwise normal. There were herpetic crusts around the nose and over the lips. The

8 Van Wering, F. Over een geval van besmetting met den necrosebacil van Jensen, Nederl. Tijdschr. v. Geneesk. 1: 2892 (June) 1923.

tongue was moderately coated and the oral mucous membranes showed injection and were dry. The pharynx was deeply inflamed especially over the anterior pillars on the posterior wall a mucopurulent exudate was present. The tonsils were small but inflamed. The lungs were clear with from 22 to 24 respirations a minute. The heart was normal. The blood pressure was 110 systolic and 50 diastolic. The abdomen was unremarkable except for striae albae of pregnancy. The results of rectal and pelvic examinations were negative. Extreme pain was felt in the left hip during flexion of the thighs. Palpation over the left hip joint revealed tenderness over the region posterior and superior to the trochanteric eminence. There was also some pain on pressure just below the left inguinal ligament. Extension and flexion of the left thigh produced pain referred to the hip but no pain followed internal and external rotation of the limb. Pain was present on palpation over the left sacro-iliac joint. The reflexes were normal.

Laboratory Observations—The urine was yellow and cloudy and contained a slight trace of albumin and a moderate number of hyaline and granular casts a few leukocytes and an occasional red blood corpuscle. The hemoglobin content of the blood was 85 per cent (Sahli) the leukocyte count 16,400. The smear was normal. The differential count showed polymorphonuclears 92 per cent lymphocytes 6 per cent and large mononuclears 2 per cent. The nonprotein nitrogen was 45.8 mg per hundred cubic centimeters. The blood Wassermann reaction was negative. The result of the Widal test was negative. A culture of urine contained *B. coli*. Cultures from throat smears showed about 10 per cent hemolytic streptococci. Three blood cultures gave no growth to the time of death. Stereoroentgenograms of the pelvis (taken the day after admission) showed nothing definite except for slight irregularities and haziness along the left sacro-iliac joint and generalized clouding of the left hip joint. A flat plate of the chest showed only accentuated hilum shadows on the right. Exposures taken three days later (fourth day after admission) showed shadows of increased density near the right hilum on a level with the seventh and eighth dorsal vertebrae not typical however of consolidation and stereoscopic photographs of the sacro-iliac joints showed some fuzziness but no definite clearcut changes (fig. 1).

Course—On the morning of admission the patient had a temperature of 40.4 C (104.7 F) a pulse rate of 122 and a respiration rate of 28. The first impression was that she had a streptococcus sore throat septicemia pneumonia or a septic process involving the left hip joint. The orthopedic consultant who saw the patient on the day after admission thought the physical observations suggested involvement of the left sacro-iliac joint the signs however were not at all typical. Slight fulness and tenderness were apparent over the left sacro-iliac joint and pain in the inguinal region on flexion of the straight limb beyond 45 degrees no tenderness was felt on deep pressure in the left lower quadrant of the abdomen. On the third day the patient was more toxic and at times delirious, her condition suggesting pneumonia despite the absence of signs in the chest other than accentuated breathing in the upper right region. The local signs in the left sacro-iliac region were more definite with tenderness in the left lower quadrant. The orthopedist's decision was to postpone surgical intervention until pneumonia was ruled out. At this time the skin assumed an icteric tint. The temperature remained sustained around 39 C.

During the next two days the patient became worse. The temperature was 41.3 C (106.3 F) the pulse from 130 to 160 and the respirations from 22 to 44. The local signs around the sacro-iliac region were accentuated and then they completely disappeared. Surgical procedures were then deemed unnecessary.

The roentgenologist reported only slightly increased shadows in the ilium region on the right. Meanwhile over the coccyx two small gangrenous ulcers containing minute hemorrhages had appeared. Lumbar puncture showed normal spinal fluid. Repeated examinations by various medical consultants failed to yield any additional information. Daily leukocyte counts ranged between 19,000 and 23,000 per cubic millimeter. Several examinations of the urine gave the same results as on admission. Several blood smears were similar, except for a marked decrease in the number of platelets seen. From day to day, the patient became more toxic. The hyperpyrexia, chills, jaundice and irregular irrational state continued. Fluids were



Fig 1 (case 1) —Roentgenogram of pelvis, Dec 28, 1929. A rarefied "string" of air in the soft tissues can be seen medial and anterior to the neck of the left femur and the lesser trochanter. The left sacro-iliac and hip-joints show only slight general cloudiness.

forced, and infusions and sedatives given. On the fifth day, a definite friction rub, accompanied by fine rales, was heard over the right side of the chest posteriorly from the seventh to the ninth ribs about 5 to 6 cm. from the vertebral margin. A blood smear showed polymorphonuclears 93 per cent with many young forms, myelocytes 2 per cent, lymphocytes 3 per cent, large mononuclears 2 per cent and no blood parasites.

On the sixth day, the patient was still worse. Deep jaundice set in. The icteric index was 125 (12.5 mg per hundred cubic centimeters bilirubin). The local signs in the region of the hip had disappeared or were masked by the toxic state of the patient. On the seventh day, it was decided to employ transfusion. At this time the blood showed leukocytes 10,400, hemoglobin content 110 per cent (Sahli), red cells 5,500,000 and a diminished number of platelets in the smear. The patient had become moribund, with a temperature of 41.7 C (107.1 F), cyanosis and a rapid, weak pulse. Cardiac stimulants were ineffective. As a transfusion was being prepared, death occurred at 2:20 p. m., Dec. 31, 1928.

Antemortem Diagnosis—General sepsis, ? pyelophlebitis, ? Weil's disease.

Necropsy—Postmortem examination was performed by Dr. Khun Shribishay one hour after the patient's death. The anatomic diagnosis was: Retroperitoneal abscess (left) involving sacro-iliac joint, hip joint and upper part of leg, infarction of lungs with abscess formation, fibrinous pleuritis, acute bronchitis, hemorrhagic enteritis, adhesive salpingitis, acute splenic tumor, slight cloudy swelling of the liver and kidneys, jaundice, skin hemorrhage (coccygeal region) and ecchymoses (abdomen and thighs).

The body was warm and emaciated, and the skin of a deep icteric color. Over the coccygeal region was a bluish-red hemorrhagic area of induration measuring 10 cm in diameter. The sclerae were also icteric. There was no lymphadenopathy. The serous surfaces were generally smooth and had an icteric tint. There was no excess of fluid in the peritoneal, pericardial or pleural cavities. There were fibrinous pleural adhesions over the lateral and posterior aspect of the lower and middle lobes of the right lung. In this region, the pleural surfaces were roughened and showed injection. The liver margin extended 1 cm below the right costal border in the midclavicular line.

The heart weighed 200 Gm and was normal, except for several hemorrhagic spots over the endocardium. The blood in the heart chambers was a thin, pale red liquid and clotted slowly.

The right lung weighed 370 Gm, the left 250 Gm. The right lung was soft and bluish gray, except for a large area about 8 cm in diameter over the middle portion externally and a few areas varying from 1 to 3 cm in diameter over the basal margins. These areas were deep red and firm, appeared to have soft gray centers and were covered with a roughened coat of yellowish fibrin. Those at the base of the lung appeared to be typical abscesses. Many petechial hemorrhages were scattered over the entire lung surface. The peribronchial lymph nodes were slightly enlarged, softened and bluish-gray. The bronchi contained a yellowish-gray mucopurulent exudate, and the mucosa showed injection, and was swollen and yellowish pink. Sections of this lung showed several large and small areas of infarction throughout the middle and lower lobes. The largest one corresponded to the previously mentioned firm area over the middle portion of the lung, and extended inward about 6 cm from the lung surface. This infarct was firm, had a deep red, elevated surface with a grayish-pink necrotic center. Mucopurulent material exuded on pressure. The smaller infarcts were similar. Over the base of the lung toward the margins were a few additional abscesses, varying from 1 to 2 cm in diameter, containing thick, greenish-gray pus, and having thin, well-defined walls. No thrombi were seen in the larger vessels adjacent to the abscesses or infarcts. Other portions of the lung were soft, pinkish-gray, moist and crepitant. The left lung also was bluish gray, and its surfaces were mottled with many petechial hemorrhages. A few translucent, yellow, fibrinous patches were scattered over the basal margins. With the exception of a large infarction, the left lung resembled the right.

The spleen was enlarged (240 Gm.), and its capsule was tense and smooth. On section, the soft bulging appearance of acute splenic tumor was seen.

The liver, pancreas, appendix, brain and blood vessels were normal.

The stomach contained dirty black, viscous mucus. The mucous membrane of the entire gastro-intestinal tract was normal, except for a portion of the ileum 15 cm. in length a half meter from the cecum. Here the mucosa, especially about the rugae, was deep red, swollen and covered with bluish-gray necrotic tissue.

The transition between the cortex and medulla of the suprarenal glands was indistinct, and the medulla seemed rather soft.

The pyramids of the left kidney were red, showed injection and were sunken. Otherwise, the kidneys, as well as the bladder and ureters, were normal.

The uterus was of normal size. It was hemorrhagic in a small area (old placental site) in the fundus. The lateral half of the left fallopian tube was swollen and soft and showed injection. The fimbria was also swollen, deep red and adherent to the ovary by a small cystlike sac containing translucent, yellowish mucus. The broad ligament and ovary were normal. The right adnexa and the vagina were normal.

In the retroperitoneal tissues behind the left kidney was a large, swollen, jelly-like abscess containing thin, pinkish-gray pus with bluish-gray necrotic tissue. This abscess had no definite wall, but extended downward along the left psoas magnus fascis and intermuscular connective tissue septums. The left psoas magnus muscle was swollen and softened and the muscle tissue in places appeared bluish, soft and necrotic. From this muscle, the abscess was traced into the left pelvic connective tissue and muscle fascia downward into the left sacro-iliac and hip joints, and half the length of the femur. The left hip joint when opened, seemed to contain gas under pressure. The hip joint capsule and periosteum were bluish and necrotic. The joint cavity was distended with thin, bluish-gray pus possessing a peculiarly foul odor. The right hip joint was not investigated, but the structures and fascias of the right side of the pelvis seemed normal. The lumbar vertebrae, sacrum and upper end of the left femur showed no abscesses or inflammation. There were no thrombi in the left common iliac, femoral or ovarian veins.

Microscopic Examination—Sections of the heart showed some swelling and opacity of the muscle fibers. In the lungs were many abscesses of varying size. The walls of the larger abscesses consisted of newly formed fibrous tissue rich in young blood vessels and infiltrated with polymorphonuclear leukocytes. These walls were covered with necrotic cellular debris and clumps of bacteria. The small abscesses had no definite walls and consisted of leukocytes and clumps of bacteria. The alveoli and bronchial walls were engorged with blood, and in several areas contained an acute cellular exudate. There was marked dilatation of the intact alveoli.

The spleen showed blood engorgement in the sinuses and stroma, increase in leukocytes and plasma cells, and hyperplasia of the mononuclear elements of the splenic tissue. The liver cells were swollen, and the cytoplasm opaque and finely granular.

Sections of pancreas, ovary, brain and pituitary were normal, also the uterus, except for hemorrhage into the mucosa in the region of the placental site.

The intestine showed diffuse hemorrhages into the mucosa.

The suprarenal glands showed a scattering infiltration with clusters of small lymphocytes and plasma cells. In places beneath the capsule there were small necrotic cells surrounded by polymorphonuclear leukocytes.

The kidney tubules showed cloudy swelling. The capsule was thickened and fibrotic in places with cellular infiltration, consisting mainly of lymphocytes.

The left fallopian tube showed a diffuse cellular invasion into the submucous and muscular coats.

Sections of the psoas muscle revealed abscess walls covered with necrotic, poorly preserved, bluish-staining, homogeneous material and polymorphonuclear cells. Adjacent muscle fibers were swollen, opaque and indistinct. Along the muscle septums much acute cellular exudate and fibrin were seen. Edema and hemorrhage were prevalent.

Sections of the hip joint capsule showed necrosis, hemorrhage and polymorphonuclear infiltration into the serosa. There were many clusters of bacteria in the blood vessels and probably in the lymph channels of the submucosa. Diffusely scattered clumps of coarse, dark brown material were seen everywhere.

Bacteriology—From the psoas muscle, pus and lung infarcts, small, short, gram-negative bacilli were seen on smear, and from these materials and the blood, pure anaerobic cultures of a gram-negative, thin, pleomorphic, filamentous coccobacillus were obtained. Antemortem blood cultures also yielded a similar organism, but not before death. A gram-positive diphtheroid grew out in the aerobic cultures of the lung infarct.

CASE 2—History—F. C. G., a white man, aged 64, a clothing cutter, was admitted to the surgical service, emergency division, of the Strong Memorial Hospital, Feb. 13, 1929. He chiefly complained of sore throat, chills, fever and dyspnea. The onset had occurred three days before when the patient complained of a sore throat. At that time, his neck was swollen, and the left tonsil seemed distended and swollen to almost midway in the pharynx. The next day the family physician was called. He thought the patient had quinsy. During that evening, chills and fever appeared. By the following morning (the day of admission), the temperature was normal, but the patient's wife noticed that he had great difficulty in breathing. His physician, when summoned, advised immediate hospitalization.

The patient had been troubled with hoarseness, at intervals, for the previous twenty years, and had had a growth removed from his pharynx by a local specialist prior to this time. He had gonorrhea in his youth. He had a bilateral inguinal hernia repaired in this hospital in 1927. At that time, the diagnosis was chronic myocarditis and general arteriosclerosis.

Physical Examination—On admission, the patient was breathing with great difficulty. The temperature was 36.5 C (97.7 F), the pulse rate was 96, the respiration rate 30. There was retraction of the chest during respiration, and there was swelling of the neck, with (crepitant) emphysema over the left side down to the clavicle. The lungs seemed clear. The impression of the physician who admitted the patient was that there was a perforation of some air passage, probably the larynx or the trachea. A surgical consultant confirmed the observations already noted. The swelling of the neck was diffuse, involving the whole left side. The left tonsil was moderately enlarged, and both arytenoid cartilages and the aryepiglottic fold and the false vocal cords were swollen. The right true vocal cord was moderately swollen and showed injection, the left could not be seen. Percussion of the chest revealed no areas of dullness but both sides were slightly hyperresonant. Sibilant râles were heard in both bases. The clinical impression was emphysema and abscess of the left side of the neck possibly secondary to a left peritonsillar abscess. Immediate tracheotomy was advised.

Laboratory Observations (Emergency)—The blood showed red blood cells, 4,850,000, hemoglobin content (Sahli), 100 per cent, leukocytes, 4,900 per cubic millimeter. The differential count showed polymorphonuclears, 83 per cent, lymphocytes, 3 per cent, and mononuclears and transitions, 14 per cent. The smear revealed practically no mature polymorphonuclears, nearly all being in the metamyleytic and related forms. A roentgen ray picture of the chest showed shadows of decreased density in the left supraclavicular and left cervical region, suggesting



Fig 2 (case 2) —Roentgenogram of chest, Feb 13, 1929. 'Pocketed rarefactions' due to interstitial emphysema can be seen in the left cervical and clavicular regions to a point several centimeters below the clavicle.

interstitial emphysema of the soft parts probably from a rupture of either the upper portion of the esophagus or the larynx (fig 2).

Course—The patient was taken to the operating division, where, under procaine hydrochloride anesthesia, a tracheotomy was performed. A low collar incision was made, and the skin fascia and platysma muscle were deflected. An abscess containing a foul, greenish-brown, watery pus was encountered beneath the fascia of the left sternohyoid and sternothyroid muscles. A smaller abscess was present on the right. A tracheotomy tube was inserted through an incision in the second

and third cartilages. Immediate respiratory relief for the patient resulted. Petrolatum gauze pack and dry dressing were applied.

Despite the immediate respiratory relief following the operation, the patient's condition was considered critical. Steam inhalations and rectal infusions of 5 per cent dextrose were given. Early the next morning the pulse became weak and rapid, the respirations rapid and labored, and the temperature rose to 39 C (102.2 F). Percussion dulness and râles were noted at both lung bases. Ephedrine, epinephrine and caffeine were administered without improving the condition of the patient, and he expired at 9 a. m. Feb 14, 1929.

Antemortem Diagnosis—Abscess and emphysema of neck

Necropsy—Postmortem examination was performed by Dr. George H. Whipple four hours after the patient's death. The anatomic diagnosis was Retropharyngeal abscess with gangrene and extension into the peritracheal and subcutaneous tissues as well as the upper anterior and posterior mediastinum, operative incision and tracheotomy wound, acute purulent pleurisy, both lungs, acute fibrinous pericarditis, acute tracheitis and bronchitis, bronchopneumonia, pulmonary edema, emphysema, fibroid apical scars, both lungs, healed surgical incisions (inguinal herniae), arteriosclerosis, diverticulum of cecum.

The body was rather slender. It was discolored by livor mortis and rigor was well marked. The neck, especially on the left, was considerably swollen, and gave diffuse crepitation. The recent surgical incision extended about 10 cm. around the neck somewhat below the cricoid cartilage. In this wound was exposed a dirty, greenish-brown, gangrenous area from which a foul, greenish, watery pus exuded, and an opening (tracheotomy incision) was seen entering the trachea. Scars of the repair of the inguinal hernia were present. The peritoneal surfaces were normal, except for a few adhesions between the sigmoid and the left obliterated inguinal sac.

When the manubrium was removed, the area of inflammation with gangrene extended down about 2 inches (5 cm.) below the manubrium into the anterior mediastinum. Below this and extending over the pericardium, there was edema with some infiltration of the wet tissue with gas bubbles. The pericardial sac was involved in this acute process, which had extended through it. The sac was thickened and its inner surface slightly roughened, showing a little fibrin and mottled reddish spots. A slight excess of pericardial fluid was present. In the left pleural cavity there was about 100 cc. of turbid serous fluid, and some purulent exudate was adherent to the posterior portion of the left lung. This was true also of the right lung. A few old apical adhesions were present.

The heart weighed 370 Gm. The epicardium anteriorly showed early pericarditis, with some injection and a few ecchymotic specks and grains of fibrin. Except for small patches of arteriosclerosis on the aortic valves and in the coronary arteries, the heart was normal.

The left lung weighed 600 Gm., and the right 480 Gm. The inflammatory process from the mediastinum extended into the tissues about the left hilum. The bronchi showed injection and contained some purulent exudate. The pulmonary vessels were normal. In the left lung, the upper lobe was somewhat moist and, on section, was mottled with a greenish color. There was no consolidation. There were some areas of collapse alternating with areas of emphysema in the left lower lobe. The wet red lung tissue seemed to possess a little cellular exudate, but no well marked areas of consolidation. Practically identical observations were made in the right lung. In the lower lobe of the latter were a few indefinite grayish areas suggesting early bronchopneumonia.

The spleen, pancreas and suprarenal glands appeared normal

The liver weighed 1,700 Gm. It possessed a somewhat yellowish cast when viewed through the capsule

The gastro-intestinal tract was normal, except for several small submucous hemorrhages in the ileum and a diverticulum 2 cm. in diameter in the cecum

The kidneys weighed 150 and 160 Gm. They contained a few small cysts but otherwise were normal

The bladder and prostate were normal, except for slight enlargement of the latter

The vascular system showed a moderate amount of arteriosclerosis in the aorta

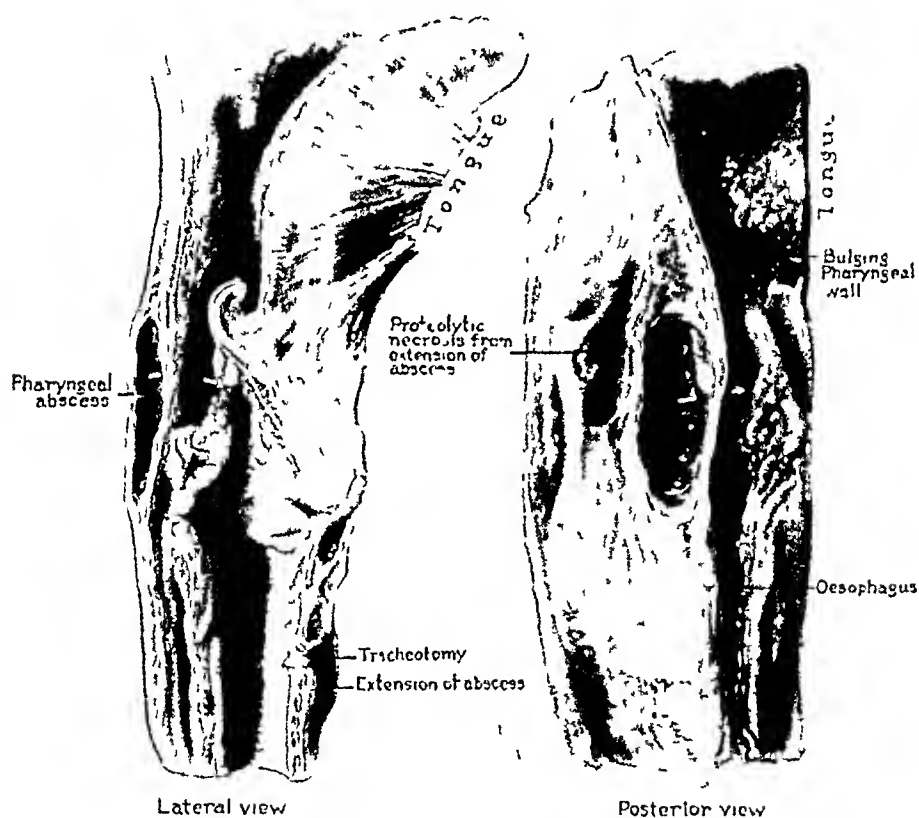


Fig 3 (case 2) —Lateral and posterior views of the fixed museum specimen of organs of the neck. The large pocket of the retropharyngeal abscess, the opening from the pharynx, the proteolysis of the adjacent tissues and the edema of the pharyngeal wall, epiglottis and subepiglottid structures should be noted

Organs of the Neck The thyroid, embedded in a mass of gangrenous semi-digested material, appeared intact and on section, normal. The large vessels were clear. When the esophagus was opened from behind it appeared to be normal as far as the region just above the cricoid cartilage (fig 3). Here to the left of the midline there was a discolored area about 5 cm. in length. Behind this area were communicating pockets showing necrosis and greenish slough. One of these pockets communicated by a small opening with the pharynx. The tonsils were normal. The tissues on the left side of the throat, including the soft palate, were edematous, having a jelly-like, semitranslucent appearance. The edema was

marked on the left side of the epiglottis and in the aryepiglottic folds. The right side of the epiglottis was relatively normal, as well as the remaining pharyngeal structures on the right side. The tongue was normal. The trachea was normal, except for the tracheotomy opening. On the left there was marked edema with induration and communicating pockets of necrosis infiltrating the tissues adjacent to the pharynx and the operative incision previously described. The retropharyngeal space was almost completely involved in this process extending down as far as the arch of the aorta.

Microscopic Examination—Some sections of the lungs showed anthracosis and areas of atelectasis, some showed edema and clusters of bacteria in the alveoli and exudate of polymorphonuclears, and others, pleural inflammation in which masses of bacteria were conspicuous. In the mediastinum there was persistent thymus tissue with cystic areas and acute inflammation with colonies of bacteria. The aorta showed atheroma with subintimal degeneration, the kidney, a few scattered arteriosclerotic scars, the stomach, a slight degree of chronic gastritis, the thyroid, a few small adenomas, and the prostate, some hypertrophy and numerous corpora amylacea. The suprarenal glands, spleen and pancreas appeared normal.

Microscopically, the tissues of the neck and pharynx showed extensive necrosis of the muscle fibers with hyaline change and a typical cellulitis with masses of bacteria. One vessel showed inflammation of the wall extending inward almost into the subintimal tissue. No thrombi were present. The thyroid showed no inflammation.

Bacteriology—From the foul, greenish pus from the neck tissues, *Pneumococcus* type IV was identified, a nonhemolytic, anaerobic, short-chain streptococcus was grown, and a gram-negative, thin, pleomorphic, filamentous, anaerobic coccobacillus was isolated. A similar gram-negative, thin, pleomorphic, filamentous, anaerobic organism was obtained from cultures of the pericardial purulent exudate, accompanied by an occasional anaerobic, nonhemolytic, short chain streptococcus. A gram-positive bacillus was present in the smears of the pus from the neck, but did not grow out in cultures. Spore-bearing organisms were not present. The gram-negative bacilli appeared in the smears as small short rods having deeper staining terminal polar bodies. Spirochetes were not seen in the smears from the subcutaneous abscess.

BACTERIOLOGY OF *ACTINOMYCES NECROPHORUS*

Original cultures of material obtained at both necropsies were made in a series of duplicate poured plates of 5 per cent (rabbit) blood agar for observing parallel growth of aerobic and anaerobic organisms. Anaerobic cultures were maintained in the jar described by Brown.⁹ In case 1, *Actinomyces necrophorus* was secured in pure culture, except for the gram-positive, aerobic diphtheroid, probably a contaminant derived from the lung infarct. In the second case, the wound constituting the portal of entry (retropharyngeal abscess) gave ready access to other (secondary) organisms. These bacteria were present in small numbers, as the smears and cultures indicated.

⁹ Brown, J. H. An Improved Anaerobe Jar, J. Exper. Med. **33** 677, 1921.

It has been pointed out that the most frequent entry of *Actinomyces necrophorus* into the body is either through the skin or the mucous membranes. Harris and Brown¹⁰ found the uterus the portal of entry for infection with *Act. pseudo-necrophorus*, an organism similar in morphology to *Act. necrophorus*. The relatively normal 5 months old placental site found at necropsy in case 1 was therefore at first suspected as the origin of the infection. After reviewing the observations at necropsy, weeks later, the 15 cm long bluish, hemorrhagic ulceration of the lower ileum appeared to have been the more probable portal of entry. In case 2, the small ulcerous opening into the retropharyngeal abscess was obviously the most conspicuous connection between mucous membranes and the extensive proteolytic process. Unfortunately, smears and cultures were not obtained from uterine intestine or pharynx, to check the bacterial flora at these points.

Studies on the morphology, cultural characteristics and serology of the strains of *Act. necrophorus* isolated in these two cases were made unfortunately, without an acquaintance with the organism. No strains were available from any source for comparison. But the identification of the organism was confirmed through the kindness of Dr J. Howard Brown,¹¹ who examined strains from each case. On the other hand Dr W. A. Hagan,¹¹ of Cornell, expressed some doubt as to whether these were cultures of true *Actinomyces necrophorus*. The organisms isolated from these cases however, appeared to satisfy most of the essential criteria used to identify *Act. necrophorus*.

Morphology and Staining—The organisms as obtained from the pus from human tissues appeared as short, bipolar gram-negative, minute coccobacilli with rounded ends or as slightly longer solid-staining rods. In one instance, they were not distinguishable from the cellular debris until another search was made. Then there were discovered also occasional weblike clusters of gram-negative strands and longer rods having fairly regularly arranged, deeper staining coccoid bodies. In cultures, the organisms were nonmotile and occurred in the most bizarre forms. In addition to those just described, they were seen as long filaments in great tangled masses with fairly regular, deep-staining coccus-like granulates (fig 4). The filaments sometimes extended nearly across the oil immersion field. In some, especially the shorter rods, the staining was more irregular assuming the appearance of biconcave partitions of variable thickness, separating slightly swollen or bulbous compartments. In these, the ends were frequently pointed,

10 Harris, J. W., and Brown, J. H. Description of a New Organism That May Be a Factor in the Causation of Puerperal Infection, *Bull. Johns Hopkins Hosp.* **40**: 203, 1927.

11 Personal communication.

like the bow of a narrow boat, and terminal polar bodies were usually present. The filamentous forms were more numerous on solid mediums, at times stained solidly, or as segments with empty compartments, some of which were bulbous (fig 5). The organisms took the aniline stains, and with methylene-blue, solid-staining diphtheroids or forms with club-shaped extremities were seen. In the older cultures and occasionally in the young, the pleomorphism and "vacuole" formation were most spectacular. Spores were not formed. Large "trunks" were seen, from



Fig 4—Photomicrograph of methylene blue stained smear from a two to three day old blood agar culture of *Act. necrophorus* A-718 M showing long curled, filamentous forms with pleomorphic short rods

which small branches or "twigs" appeared to radiate. The deep-staining granules were arranged irregularly near the periphery of the "trunk" and as small cocci filling the "sheath" of the branches. A terminal polar body was commonly present in each branch. Large clubbed filaments with smaller granules were sometimes seen. Acute fusiform dilatations were occasionally present in the filaments, or the rods some-

times assumed a short swollen form in which the polar staining was in the form of a thin crescent. Occasionally terminal bulbous enlargements were present. Schmorl's excellent illustrations are characteristic of many of the morphologic variations observed in these strains of *Act. necrophorus*.

Cultural Characteristics—On appropriate mediums kept anaerobically at 37 C, *Act. necrophorus* survived as long as five months. Optimum growth was obtained on mediums containing ascitic or hydrocele fluid.



Fig. 5—Photomicrograph of methylene blue stained smear from a two to three days old blood agar culture of *Act. necrophorus* A-718 M, showing several filaments with cross-striations and bulbous compartments.

The organism was an obligate anaerobe. Growth in tubes of cooked meat (Douglas' tryptic broth) medium with a petrolatum seal was accompanied by a moderate production of foul gas without appreciable digestion of the particles of meat. At first in this medium there was a flocculent, fuzzy growth which later settled to the bottom of the tube, where it had a pale blue appearance among the particles of meat. On

5 per cent blood agar plates a wide zone of beta hemolysis appeared in from 24 to 48 hours (fig 6) with smooth convex-topped nearly transparent surface colonies having fairly regular edges and a slightly brownish center. Three-day colonies measured from 2 to 3 mm in diameter. Older surface colonies showed serrated or fuzzy filamentous edges. These projected radially from a darker rim zone separated by a lighter intermediate zone and were surrounded by a finely granular brownish area superimposed on the clear, hemolyzed plate (fig 7). Such colonies measured between 3 and 7 mm in diameter. A foul odor was also produced by the growth on blood agar plates. Colonies growing deep in blood agar tubes or plates appeared as yellowish-gray, dirty, biconvex lenses, surrounded by hemolysis and a brownish discoloration.

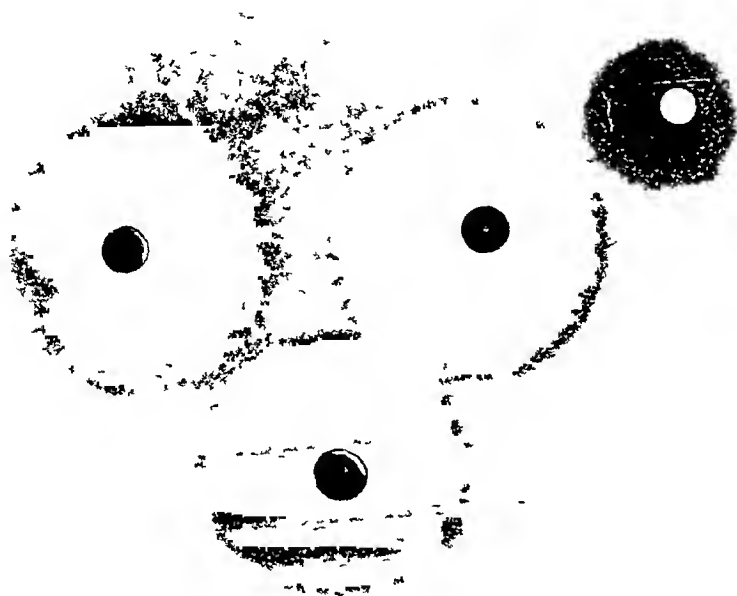


Fig 6—Surface colonies of *Act. necrophorus* A-718 M, on a blood agar plate, from two to three days old. The wide zone of hemolysis should be noted.

The fermentation tests done with 1 per cent “sugars” either in tryptic broth or in 10 per cent ascitic agar with Andrade’s indicator, agreed uniformly. With dextrose, sucrose, lactose and mannite there was growth with acidification (“fermentation”), and in the petrolatum-topped tubes of liquid medium, production of gas. With xylose there was no fermentation or apparent growth, but gas was produced in salicin. A small amount of gas was produced in plain tryptic broth. No growth occurred with plain agar, gelatin, milk or inulin serum. Nitrates were not reduced. Indol was formed both in cooked meat and tryptic broth.

While no final tests were done to determine the viability of the organisms colonies exposed to air for forty-eight hours contained living organisms. Motility was not demonstrated.

PATHOGENICITY

The virulence of *Act. necrophorus* in man is self-evident from the two cases reported. Rabbits, guinea-pigs and mice were chosen for

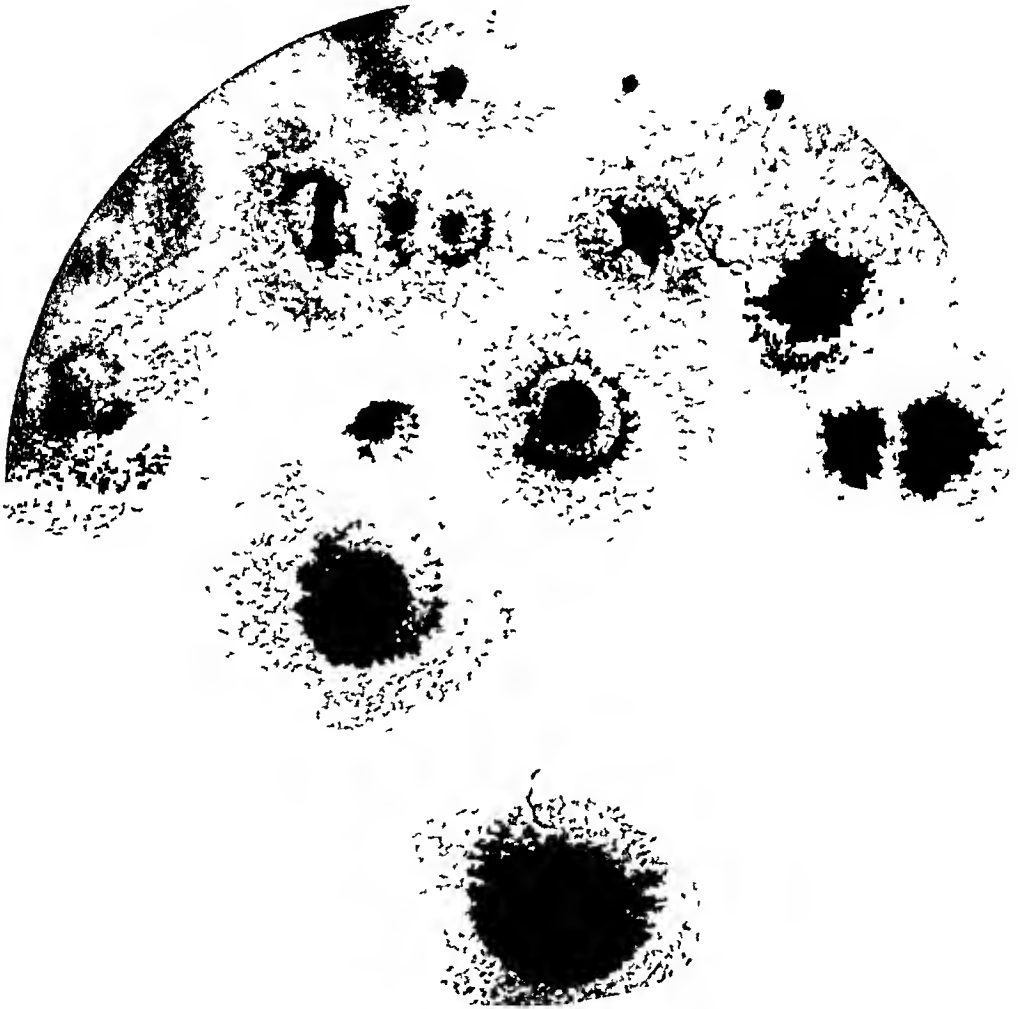


Fig 7—Surface colonies of strain A-718M on a blood agar plate, from seven to eight days old. The dense center, lighter intermediate zone, radial serrations at the peripheral portion of the colonies and the smudging of the hemolyzed area just beyond should be noted.

use in testing the pathogenicity of the organism for animals. Blood taken from the patient in case 1 at necropsy was injected into a guinea-pig the next day (being kept in the cold room over night), 0.5 cc being injected intraperitoneally. The animal appeared lethargic for several days, but at necropsy, two and a half months later, was normal. Diluted

psoas pus from the same patient was injected 0.25 cc intracutaneously, into a guinea-pig. A small hemorrhagic tumor resulted, but this animal also was normal at necropsy, two and a half months later. A guinea-pig inoculated subcutaneously with 0.5 cc of a seven-day broth culture of strain A-718M developed a local tumor, which rapidly subsided, leaving no evidence of inflammation thirty-seven days later at necropsy. A white mouse into which 0.5 cc of the same material had been injected intraperitoneally died three days later, weighing one fifth less and having a greenish, fibrinous peritonitis with a foul odor.

Rabbits were susceptible to infection with *Act. necrophorus* (strain A-718M), as table 1 shows. Subcutaneous inoculations (rabbits 88 and 91) were followed by an intense inflammatory process with gangrene,

TABLE 1—*Pathogenicity of Act. Necrophorus, Seven-Day Broth Culture (Strain A-718M) and Filtrate, for Rabbits*

Rabbit	Weight, Gm	Inoculation		Weight Loss, Gm	Lesions in Life	Died or Was Killed	Days	Pathologic Changes at Necropsy
		Location	Amount, Cc					
88	2497	Subcutaneous, abdomen	1.0		Abscess	Killed	82	None
91	2383	Subcutaneous, ear	0.1		Abscess	Killed	32	None
85	3114	Left knee joint	0.2	624	Sick	Killed	24	Necrosis of soft tissues and bone
86	2837	Intravenous	1.0	681	Sick	Died	11	Intercurrent pneumonia (?), early liver abscesses
87	2887	Intravenous	1.0 + 1.0 cc immune rabbit serum	590	Sick	Died	12	Necrobacillosis of liver
95	3972	Intravenous	2.0	794	Sick	Died	11	Necrobacillosis of liver, jaundice, splenic tumor
89	2383	Intravenous	1.0 (filtrate)	113		Killed	32	None
90	2496	Intravenous	1.0 (filtrate) + 1.0 cc immune rabbit serum	340	Sick	Killed	32	None

formation of abscesses (fig. 8), rupture, sloughing and spontaneous healing. This was most marked following injection into the abdominal wall. Intravenous injection of cultures (rabbits 86, 87 and 95) was followed by progressive loss in weight, profound toxemia and death. Jaundice, delayed clotting of the blood and specific abscesses of the liver were found at necropsy. The injection of filtrate resulted only in a slight immediate and temporary loss in weight. Equal quantities of "immune serum" (table 2) injected simultaneously with cultures and filtrate had no perceptible effect, other than that which might be represented in the greater loss of weight in the animal employed for this experiment than occurred in the rabbit into which filtrate only had been injected. No local injections of filtrate were attempted nor was the pathogenicity of strains A-650 Bld, A-650L or A-650 Med determined.



Fig 8—Large, blackened gangrenous abscess three days after subcutaneous injection of a broth culture of *Act. necrophorus* A-718 M into a rabbit



Fig 9—Multilocular abscesses resulting from the injection of 0.2 cc of a culture of *Act. necrophorus* A-718 M into the left knee joint of a rabbit

TABLE 2.—*Dilution of Agglutinins and Cross-Agglutination in Serum of Rabbits Immunized Against Act Neophilus 1-650 Bld and 4-718 M*

Rabbit	Antigen		Dilutions of Immune Serum										
	Immunization	Agglutination	1 2,500	1 5,120	1 10,240	1 20,480	1 40,960	1 81,920	1 163,840	1 327,680	1 655,360	C	
370	A 670 Bld	A 670 Bld (case 1)	++	+++	++	++	+	0	0	0	0	0	
370	A 630 Bld	A-718 M (case 2)	++	+++	++	0	0	0	0	0	0	0	
377	A 630 Bld	A 630 Bld	+++	+++	+++	+++	+++	+++	+++	++	+	0	
387	A 670 Bld	A 718 M	+++	+++	++	+	0	0	0	0	0	0	
389	A 718 M	A 670 Bld	+++	+++	++	±	0	0	0	0	0	0	
389	A 718 M	A-718 M	+++	+++	+++	+++	++	+	0	0	0	0	

The most spectacular production of lesions was obtained on infecting rabbit 85 in the left knee joint. Inflammation, tenderness and limitation of motion resulted, followed by the formation of tremendous multilobulated abscesses of the soft tissue (fig 9). Weakness and excessive loss of weight were present (table 1). Roentgenograms

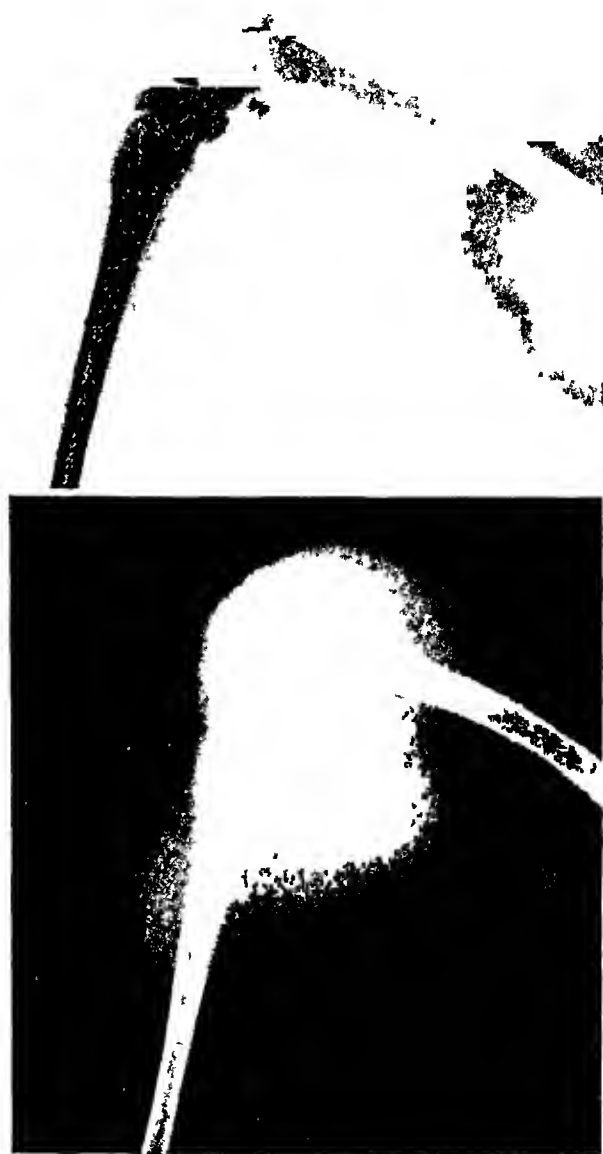


Fig 10—Lateral view of right (normal) and left (infected) knee joint region of rabbit. The abscesses of the soft tissues, the destruction of the diaphyseal portion of the bone shafts, and the periostitis following the injection of Act necrophorus A-718 M should be noted.

showed, in addition to the swelling of the soft tissue, extensive destruction of bone about the diaphyseal ends of the shafts of the femur, tibia and fibula with advanced proliferative periostitis (fig 10). No visible

change in the joint surfaces was apparent. At necropsy the large nodular fluctuant swellings incised through edematous pale semi-translucent glassy walls composed of skin muscle and fascia revealed a large amount of thick granular pus of a creamy, yellowish appearance. The odor was exactly that of Swiss cheese. All anatomic relationships were lost in the mass of multilobular abscess walls with frayed, fuzzy stringy strands of pale caseous muscle fascia and fibrous tissue. The caseous mass was tough and stringy near the walls and thinned in the center. The knee joint was involved presenting a dirty bluish discoloration and thickening. Intense destruction of bone had occurred in the diaphyseal portions of the femur tibia and fibula and the bone-marrow had a washed-out appearance. No gas was discovered. Aerobic and anaerobic cultures of the heart blood and of the contents of the abscess were made. Those of the blood were sterile and those of the abscess yielded *Act. necrophorus* in pure culture. Microscopic sections of the wall of the abscess and of the synovial membrane showed loss of cellular structure edema necrosis, clusters of blue-staining bacteria and considerable eosinophil infiltration, in the spleen there was necrosis with swelling of the splenic centers and eosinophil invasion and in the kidney extensive swelling of the tubular epithelium which had a finely granular acidophilic cytoplasm.

SEROLOGY

Rabbits were employed in an attempt to obtain agglutinins for *Act. necrophorus*. Two animals each were subjected to injections of strains A-718M and A-650 Bld. Serum taken from the animals before the injections were commenced and tested for agglutinins (in dilutions from 1:20 to 1:2560) proved negative. The injections were made in periods—four daily inoculations of gradually increasing doses alternating with four days rest. The antigens were made from three-day anaerobic broth cultures which had been heated to 60°C for thirty minutes washed twice in physiologic solution of sodium chloride and concentrated approximately five times. The amount of this antigen was 0.05 cc. at the beginning and 2.2 cc. at the end of the series of injections, thirty-three days later. The immune serum was drawn ten days after the last intravenous injection. Attempts to secure blood from rabbit 359 on the same day as from the others was unsuccessful, so that the final agglutination tests were not done with the serum of this animal.

The results are shown in table 2. A high titer of 1:655,000 was obtained with the serum of rabbit 357 when the same antigen strain (A-650 Bld) was used as had been employed in the immunizing injections. Cross-agglutination was apparent to but slightly lower titers

than those obtained with the homologous antigen. Great difficulty was experienced in securing a suspension of antigen which would not spontaneously agglutinate. After trying various vehicles, the five-day old broth cultures of both strains were successfully suspended in a phosphate buffer with a calculated pH 7.1,¹² after being washed once in physiologic solution of sodium chloride and concentrated from two to 4 times. Controls consisted of half mixtures of the antigens with physiologic solution of sodium chloride. The tests were done in the water bath at 56 C for two hours.

COMMENT

Necrobacillosis in man is probably more common than previously has been supposed. Few bacteriologic textbooks mention the organism. Albrecht³ stated that "undoubted infection in man has not been proven," despite the three cases of cutaneous infection cited in this paper. If anaerobic blood cultures were made more frequently in the case of patients with obscure fevers or with pyogenic focal infections it is probable that *Act. necrophorus* would be more frequently detected. This is especially applicable in the case of patients exhibiting jaundice, as well as fever, in which the ordinary etiologic agents have not been recognized.

Dr. Lawrence A. Kolm has shown me the interesting record of a colored girl, aged 19, who was under his care in the Strong Memorial Hospital in 1926, in the Medical Service of Dr. William S. McCann.

The patient for several days had suffered with headache, sore throat, chills and fever. On admission she had much enlarged and inflamed tonsils, from which foul green pus exuded, the cervical lymph nodes were enlarged, and the conjunctiva slightly inflamed, the leukocyte count was 30,000, and the fever of an intermittent type, ranging between 38 C and 41 C (100.4 to 105.8 F). The high "spiking" fever persisted, icterus and petechial hemorrhages were detected in the sclera and conjunctiva, and the patient continued to be very ill. The case was a diagnostic puzzle for some time. Throat cultures were negative for *B. diphtheriae* and showed only about 25 per cent hemolytic streptococci. The patient developed empyema in the right side of the thorax. Operative drainage was instituted and "a large amount of gas and thick, foul-smelling, muddy colored pus" was removed. A gram-positive coccus was seen in smears and aerobic cultures of the pus. Two anaerobic cultures of this pleural effusion and four blood cultures yielded a gram-negative bacillus. This organism was small and pleomorphic, growing at times in chains and rods, it possessed a distinctly foul odor, it appeared to be moderately proteolytic, and it produced gas in dextrose and other mediums. Unfortunately, the organism was lost before it could be identified. The patient ultimately recovered.

¹² Clark, W. M. The Determination of Hydrogen Ions, ed. 2, Baltimore, Williams & Wilkins Company, 1922, p. 114.

Dr Kohn saw the cultures in cases 1 and 2 and felt that there was a strong resemblance between them and those obtained in his case. From the clinical history and the characteristics of the organism recovered in his case, it seems highly probable that the organism was *Act necrophorus*.

The presence of gas in the cellulitic tissue of the neck in case 2 was recognized clinically and by roentgen examination (fig 2). In case 1, only indefinite changes were seen in the second roentgenograms of the left sacro-iliac and hip joints (fig 1). During a careful reexamination of the films in the two cases, the roentgenologist and I found additional evidence of an infection with *Act necrophorus* in the left hip joint of the patient in case 1, which had escaped notice in the previous examination. A tract of gas medial and anterior to the neck of the femur and lesser trochanter had developed in the soft tissues. In view of the nature of the organism recovered in this case, the presence of gas is readily explained.

In case 1, it is to be noted that the first clinical impressions (the interns) proved to be nearly correct, the later desperate condition of the patient masked the true picture to the extent of leading to a subsequently erroneous diagnosis.

SUMMARY

An organism having the morphologic, biologic, pathologic and serologic characteristics of *Actinomyces necrophorus* was isolated in two fatal cases in man exhibiting some of the characteristics of infection with this organism in animals. Necropsies further confirmed the resemblance of the lesions to those due to *Act necrophorus* in animals.

Experimentally, the organism was pathogenic for rabbits and mice, and questionably so for guinea-pigs. In one animal the lesions of the joint infection as seen in case 1, were reproduced, with additional destructive changes in the bone and soft tissues.

A high titer (1:655,360) of agglutinins was obtained following periodic intravenous injections of the heated, washed, concentrated organisms into rabbits. A correspondingly high degree of cross-agglutination was secured with strains isolated from both cases.

An additional case is noted of a patient with follicular tonsillitis and empyema with some clinical features similar to those seen in case 1, from whom in 1926 Dr Kohn isolated a gram-negative anaerobic, pleomorphic bacillus in the blood and empyema pus. The morphologic, cultural and clinical characteristics of this organism warrants its presumptive classification as *Act necrophorus*.

CONCLUSIONS

Two cases of necrobacillosis in man—the fourth and fifth instances of proved infection with *Act necrophorus* in man—the only fatal cases

on record, and cases presenting hitherto undescribed types of human infection, were verified by bacteriologic study.

The organisms obtained in the two cases were shown to be practically identical.

Necrobacillosis is a disease with recognizable clinical features in man. Its potentialities for morbidity and mortality should, therefore, warrant a careful search by physicians for its presence in cases of obscure infection. Anaerobic cultures on a wider scale in the routine laboratory are therefore suggested for detecting *C. necrophorus* in cases in which human necrobacillosis is suspected.

PRIMARY CARCINOMA OF THE LUNG FOLLOWING TRAUMA*

H GIDEON WELLS, M D

AND

PAUL R CANNON M D

CHICAGO

In a recent review on the causal relation of trauma to tumors Knox¹ has emphasized the difficulties in establishing such a relation without emphasizing the evidence that has so far been presented on the positive side or the difficulty in disproving the claimed causal relation in any suspected case. The negative side of this argument is certainly the easier one to support. No matter what evidence of relationship of the trauma to the subsequent tumor may be presented there is no possible way of proving that a symptomless tumor had not already been present at the time and at the site of the injury. But that such a coincidence can account for all the cases in which a tumor has arisen at the site of a single trauma after a time interval compatible with the assumption of cause and effect is somewhat of a strain on an unprejudiced imagination. Even if many of the cases of supposed development of a tumor as a sequel of a single trauma are reported inadequately to furnish positive proof of the causal relation of the trauma this defect does not prove that the assumption of traumatic etiology was always incorrectly made.

In view of the lack of satisfactory case reports it is apparent that more data are needed and that cases presenting an apparently probable relationship between a single trauma and a subsequent tumor should be placed on record in order that they may receive consideration by future investigators of the problem. Recently through the kindness of Dr Ludvig M Loeb I have had an opportunity to study a case of primary carcinoma of the lung which falls into this category and which seems to be of especial value because the roentgen plates of the site of the injury made immediately after the injury was received show that at that time there was no recognizable evidence of malignant growth.

REPORT OF CASE

A man aged 50 in general good health was knocked down by an automobile on Sept 1, 1926. He suffered severe pain in the chest and was taken to a hospital,

* Submitted for publication Dec 3 1929

* From the Department of Pathology of the University of Chicago and the Otho S A Sprague Memorial Institute

1 Knox Leila C Trauma and Tumors Arch Path 7 274 1929

where a roentgen examination the next day revealed fracture of the left third, fourth and fifth ribs in the midaxillary line. There was also distinct evidence of traumatic injury to the lung, namely, hemoptysis and a subcutaneous emphysema extending over the entire body. The roentgen films showed no evidence of any neoplasm in the lung. The fractures healed uneventfully, and the patient seemed to be in good health until the following August, when he began to have pain in the left side of the chest. He developed a cough, and symptoms suggestive of pulmonary tuberculosis appeared, but no tubercle bacilli were found in many specimens of sputum. Repeated bronchoscopic examinations failed to reveal any bronchial growth, but roentgen films now revealed evidence of cancer in the left upper lobe with shadows in the hilum apparently dependent on metastases to the lymph nodes. The clinical course was steadily downward, with evidence of progressive consolidation in the left upper lobe. Death occurred on Aug 17, 1928, or just one year after the development of symptoms, and just short of two years after the injury to the left lung. The family history revealed that a paternal grandmother died of carcinoma of the breast and that a paternal uncle died of carcinoma of the stomach.

Necropsy—Necropsy was performed three hours after death by Dr Paul R Cannon, and disclosed the presence of a primary carcinoma of the upper lobe of the left lung, with metastases in the mediastinal and left supraclavicular lymph nodes, in the retroperitoneal periaortic lymph nodes as far down as the bifurcation, in the right suprarenal gland and both kidneys. There was a thickening and an irregularity in the third, fourth and fifth left ribs in their middle thirds from the healed fractures. No other changes of significance were found.

Examination of the thoracic contents showed that the left pleural cavity was obliterated by dense fibrous adhesions. The upper lobe of the left lung was found to be almost completely replaced, especially in the upper anterior portion, by a dense white tumor mass. This mass had infiltrated through most of the left upper lobe and diffusely through the mediastinum. There was no tumor growth in the trachea or either primary bronchus, nor in the large branches of the bronchi on either side. The entire tumor mass measured 17 cm transversely, 11 anteroposteriorly and 15 cm in the superior-inferior diameter including the involved mediastinal tissues. In the portions of the upper lobe not involved in the neoplasm the lung tissue was atelectatic and contained bronchiectatic cavities. Much fluid pus escaped from the smaller bronchi. The left lower lobe was partly compressed and partly filled with air.

The right lung exhibited no tumor nodules or other marked changes beyond hypostatic edema and some emphysematous bullae.

Gross examination indicated that this tumor arose in the periphery of the left upper lobe, rather than in one of the larger bronchi, where primary carcinoma of the lung most usually has its origin.

Histologic Structure of the Tumor—The tumor was composed of cells which generally appeared elongated, consisting chiefly of nucleus with little cytoplasm, thus much resembling sarcoma cells, but they tended to form alveoli, did not secrete collagen, and often exhibited a palisade arrangement. In no places did the cells exhibit a characteristic epithelial structure, nor did they form tubular structures, secrete mucin, or undergo keratinization. In other words, the structure was that of the type of lung tumors that has often been described in the earlier literature as sarcoma and later as mesothelioma, and which has been interpreted by some as a tumor arising from the flat epithelium of the alveoli. While it is certainly not possible to determine by the histologic character of a pulmonary carci-

noma whether it arose in the bronchi or in the alveoli, or even whether carcinomas ever do arise in the alveoli, the absence of glandlike structures or of mucin, and the tendency to formation of spindle cells resembling a sarcoma, are points that have often been mentioned as in favor of a peripheral origin of a lung carcinoma, or at least as opposed to the origin of such tumors in the mucosa of the large bronchi

COMMENT

The literature reveals few instances in which a primary pulmonary carcinoma has seemed to result from a single trauma to the lung tissue. Knox,² in her review on trauma and tumors said

A serious effort has never been made to ascribe pulmonary tumor to an injury. The case reported by Lepine was that of a man who had sustained an injury to the chest wall and who one year later developed a squamous carcinoma of the lung beneath the site of the old injury. But serious injuries to the chest are so frequent and pulmonary tumors so rare that, statistically, a causal relationship is not even suggested.

Weller,³ in his recent review on the pathology of lung tumors, said

Aufrecht considered severe trauma which "does not produce laceration of the pulmonary tissue, but only molecular disturbances of an unknown character" to be an important immediate cause of pulmonary carcinoma. Four cases which he had seen were preceded by grave trauma. One woman died of carcinoma of the right lung sixteen months after falling from a ladder and striking the right side of the chest. A man accidentally received the full weight of a beam, which he was assisting in lifting, on his left shoulder. Two years later he died of diffuse carcinoma of the upper lobe of the left lung. Georgi's blacksmith was hit on the chest by a heavy mass of iron. The third patient described by Scott and Forman had suffered severe contusions of the chest when caught in a belt. The carcinoma, however, developed on the opposite side. In Barion's fifth case, the patient gave a history of a fall from a ladder, striking the chest on a plank, shortly before the onset of pulmonary symptoms. Similar examples are to be found here and there throughout the literature (Hinterstoisson, Handford) but they are so few that one must conclude, contrary to Aufrecht, that a single episode of external mechanical trauma is practically not of importance in determining carcinoma of the lung.

The case herewith reported seems to present as nearly completely satisfactory evidence as one can hope to secure of the development of a primary carcinoma of the lung as a direct result of a single traumatism to the lung tissue. Roentgen plates of the chest made immediately after the injury show that at this time there was no evidence of a carcinoma of the lungs demonstrable by this means. There is conclusive evidence of traumatism to the lung (hemoptysis and severe subcutaneous emphysema). The interval between the time at which the traumatism was received and the appearance of symptoms of the cancer of the lung (eleven months) is entirely in harmony with the assumption that the

² Knox (footnote 1, p. 292)

³ Weller, C. V. Pathology of Primary Carcinoma of the Lung, Arch. Path. 7: 478, 1929

neoplastic growth was incited by the traumatism of the lung and the duration of life after this time (twelve months) is in keeping with the rate of growth to be expected from a tumor reaching the observed state in the first eleven months after the traumatism. Finally, the fact that the gross anatomic observations indicate that the tumor began its growth in the periphery of the lung at just the site of the injury, rather than in the large bronchi nearer the hilum where most lung cancers seem to arise is strong evidence in favor of the hypothesis that this particular cancer resulted from the traumatism to the lung tissue immediately beneath the fractured ribs.

Of course it is not possible to say that there was not already a carcinoma, too small to be detected in the roentgen film, growing in the part of the lung that was traumatized at the time of the injury. But in view of the extreme infrequency of primary carcinoma of the lung arising in the periphery of the upper lobe, to support such an explanation of this particular case requires a stretching of 'the long arm of coincidence' to the vanishing point. There never will be a case of neoplasm following traumatism in which absolute proof can be offered that the traumatism did not occur at a point where a neoplasm had already begun to grow. Absolute proof would have to be furnished by complete serial sections of the tissues at the moment of their injury. Therefore, one must approach the problem of the relation of trauma to tumor with an open mind, keeping in view always the two fundamental but opposing facts:

1. Absolute anatomic proof can never be furnished that a given tumor arising at the site of a trauma has resulted from the tissue damage or subsequent reparative proliferation of previously normal tissues.

2. It is equally impossible to prove that any tumor arising at the site of and subsequent to a trauma is not the result of tissue damage or subsequent reparative proliferation if there has been no demonstrated tumor at this site at or before the time of the traumatism.

Excessive proliferation of tissue for a considerable period unquestionably leads sometimes to the continuance of the proliferation in the form of malignant growth. There is no known reason why any reparative proliferation, whether of short or long duration, may not assume the malignant character, and hence one must be as willing to accept the principle that a single trauma may lead to malignant growth as that protracted mild traumatism may have the same end-result.

SUMMARY

A case is reported of primary carcinoma of the lung, arising in the periphery of the left upper lobe, at or about the site of a demonstrated traumatism to the lung which produced hemoptysis and diffuse subcu-

taneous emphysema. Roentgenograms made the day after the traumatism, which showed fracture of the left third, fourth and fifth ribs, gave no evidence of the existence of any neoplastic condition in the lung. Eleven months after the injury pulmonary symptoms appeared, and examination now revealed a neoplasm in the periphery of the left upper lobe at the site of the trauma, which continued to grow until death occurred twenty-three and one-half months after the pulmonary traumatism. The probable relationship of the trauma to the occurrence of the carcinoma in the lung is discussed.

Laboratory Methods and Technical Notes

THE PRESERVATION OF SPECIMENS IN COLOR

G L ROHDENBURG, M.D., NEW YORK

Until within very recent years but little advance over the technic originally described by Kaiserling has been made in the preservation of gross pathologic specimens in color. The most important of the recent contributions is that of Kerner,¹ who introduced the use of illuminating gas, and who more recently proposed the use of a silicate gel as a mounting medium.

As color changes are among the more characteristic alterations observed in diseased tissues, color retention in specimens which are to be used for teaching or purposes of demonstration is of importance. A method is here presented which has several advantages over the methods now generally in use. This method fixes color better than either the Kaiserling or the Klotz method, calls for but one solution, can be carried through in the light, gives fixation which does not fade and is economical. It is virtually a modification and combination of the methods of Klotz and Kerner.

TECHNIC

The appended formula is for approximately 1 liter of solution:

Potassium sulphate	0.5 Gm
Potassium nitrate	2.25 Gm
Sodium chloride	4.5 Gm
Sodium bicarbonate	9.0 Gm
Sodium sulphite	11.0 Gm
Sodium acetate	7.5 Gm
Chloral hydrate	25.0 Gm
Solution of formaldehyde, U. S. P.	25.0 cc
Iso-propylalcohol (technical)	50.0 cc
Water	1,000.0 cc

A glass tube which is connected with the illuminating gas supply is passed to the bottom of the container, and the gas permitted to bubble through the mixture slowly for about one hour. If the glass tube is 0.5 cm. in diameter, then one bubble every second is enough gas flow. The gas is then turned off and the container immediately closed with a tightly fitting stopper.

The specimen to be preserved is wiped free of blood debris (it is not washed in water) and placed, preferably hung suspended, in a jar sufficiently large so as not to cause pressure at any point. Approximately ten times the volume of the specimen is sufficient fixative. While the color is immediately fixed, fixation should not be for less than four days; the specimen may be left in the solution inde-

* Submitted for publication, Jan. 24, 1930.

† From the Achelis Laboratory, Lenox Hill Hospital.

1 Kerner. *Centralblatt f. allg. Path. u. path. Anat.* 36:5, 1929.

finitely It is best, before placing the specimen in the fixing fluid, to prepare it as it is finally to appear, by sewing it to sheet celluloid, which is practically invisible when the specimen is mounted in gelatin

If mounted in gelatin or a similar gel, then the used fixative is filtered and returned to the original stock If the stock solution is not used up, gas should be permitted to bubble through it for about thirty minutes once a month, or should that be forgotten, then gas should be introduced for thirty minutes at least two hours before a specimen is placed therein Specimens left in the fixing fluid do not become hard and stiff

For mounting in gelatin, the method is as follows One liter of water is brought to the boiling point, the heat is removed and 100 Gm of gelatin of exceptional purity is rapidly added in small pieces The mixture is stirred until complete solution has occurred and then from 3 to 4 teaspoonfuls of activated charcoal (I have used Darco decolorizing carbon) is added for each 100 cc of the gelatin The solution is to be stirred and kept hot for five minutes It is then filtered through a Buchner funnel with suction the mat for the filter being either washed asbestos or a piece of snugly fitting, closely woven cloth, such as linen The filtrate is refiltered until clear Coarse filter paper without suction may also be used, but with suction, filtration of one liter takes about five minutes This gives a gelatin that is water clear and practically colorless The excess fixative having been permitted to drain off and the specimen having been placed in the chosen jar, 4 cc of 40 per cent formaldehyde is added to each 100 cc of melted gelatin, and the jar filled with this mixture The resultant gel is practically irreversible

General and Historical Reviews

SICKLE CELL ANEMIA [†]

BERNHARD STEINBERG, M D

TOLEDO, OHIO

EARLY HISTORY

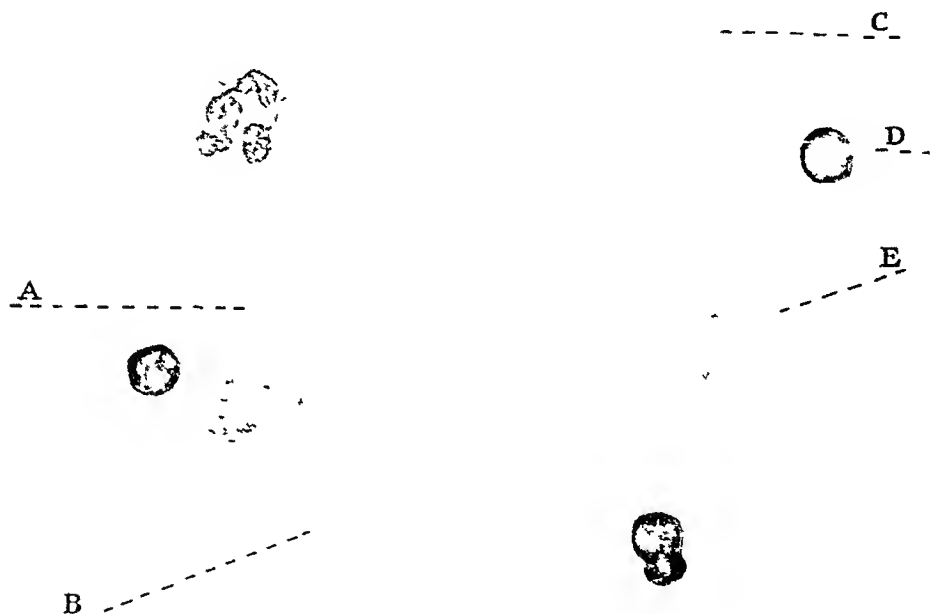
Hayem, in his book on "Blood and Its Anatomical Variations," described semilunar erythrocytes, which he interpreted as artefacts. The next mention in the French literature of this abnormality of the red blood cells was made by Seigent and Seigent, who examined the blood of a large number of natives of Algiers who are composed of Moors, Berbers, Arabs and negroes. The authors found that 51 per cent of 234 malarial native patients had "demilune" erythrocytes. Examination of the blood of 265 nonmalarial natives did not reveal any deformity of the red blood cells. These same authors found demilune red blood cells in the blood of European malarial patients and they therefore concluded that demilune erythrocytes are characteristic of the blood picture of malaria. Brumpt found demilune erythrocytes not only in the blood of malarial patients but also in that of persons suffering from various forms of intoxication. Langeran observed similar forms of red blood cells in white rats and guinea-pigs with rickets. The last author reproduced these demilune forms in other guinea-pigs and rats by injecting lead acetate into these animals. Langeran assumed that this experiment supported Brumpt's conception that the demilune erythrocytes are produced by intoxications. It is questionable whether the French writers were dealing with the same deformity of the red blood cells to which the American school gave the name of sickle cell.

In 1904 Dresbach reported the presence of elliptical red blood cells in an apparently healthy young mulatto student, who examining his own blood smear, noticed these peculiarly shaped erythrocytes which constituted 90 per cent of his red cells. No mention is made, however, of the total number of erythrocytes or the quantity of hemoglobin. Austin Flint took exception to Dresbach's statement that the mulatto was healthy and suggested that the elliptical red blood cells were poikilocytes and that the student had some form of a primary anemia. The following year, Dresbach wrote that the mulatto had had tonsillitis and then an attack of acute inflammatory rheumatism and had died of cardiac

* Submitted for publication, Nov 21, 1929

[†] From the Laboratories and the Department for Medical Research of Toledo Hospital

failure, but insisted that the symptoms and death had no connection with the elliptical red cells. It remained for Herrick in 1910 to point out in a negro patient the association of the elliptical or sickle-shaped red blood cells with a severe anemia and with certain clinical manifestations and thus establish a probable new disease entity. There is a strong probability that Dresbach's student had a condition similar to the one Herrick described. Since Herrick's paper, a fairly voluminous literature on the subject has been compiled. In 1922, Mason gave the disease the name of sickle cell anemia, which has been generally accepted.



The blood in sickle cell anemia. *A* indicates an oat-shaped cell, *B*, the sickle cell, *C*, bizarre-shaped cells, *D*, a nucleated red cell, and *E*, a reticulocyte.

INCIDENCE OF SICKLE-SHAPED ERYTHROCYTES

For thirteen years following Herrick's publication, only three additional cases of sickle cell anemia were reported (Washburn, Cook and Meyer, Mason). In the next two years the interest in the subject was further stimulated by the publications of Sydenstricker and his associates, who demonstrated that sickle cell anemia is not an infrequent disease. Both Huck and Sydenstricker found sickle cells in the blood

of patients' relatives some of whom presented few or no abnormal clinical manifestations. These observations prompted several routine examinations of the blood of apparently healthy people. Cooley and Lee examined 400 colored patients and found that 30 (7.5 per cent) of them had sickle-shaped erythrocytes but no anemia or disturbing symptoms. In Levy's series of 213 colored people, 12 (5.6 per cent) showed sickle cells and in Graham and McCarty's series of 858 negroes, 58 (6.75 per cent) showed these cells. Of Josephs' 250 colored patients, 16 (6.4 per cent) had sickle red blood cells. Cooley and Lee proposed the term sickle cell anemia for the condition in which sickle red blood cells are present without any other abnormality of the blood or apparent disturbance of health.

Sydenstricker examined the blood of 1,000 white people and was unable to demonstrate the presence of these peculiarly shaped erythrocytes. Miyamoto and Korb examined 100 white patients with similar results. Until Lawence's publication in 1927, it was generally accepted that the sickling phenomenon was peculiar either to the negro race or those with negro blood. Lawence found sickle cells in a white woman, her brother, a sister and a niece, and on examination of 102 white people, found sickle cells in the blood of three of them. Lawence's observation gives a significance to Castana's report (1925) of a case of anemia with the presence of giantocytes of a semilunar form in a white child. Stewart reported sickle cell anemia in a child whose mother was Cuban without any known negro blood and whose father was white. The probability that this disease is not limited to the negro race is further strengthened by Cooley and Lee's report of sickle cell anemia in a Greek family.

THEORIES OF THE FORMATION OF SICKLE-SHAPED ERYTHROCYTES

Following the recognition of the sickle-shaped erythrocytes, much speculation was aroused regarding their formation and origin. Although Emmel was the first to observe the presence of the sickle forms in the blood of a father and daughter, the conception of the sickle cell trait as familial and hereditary originated with Huck who had the opportunity to examine members of three generations of one family. Huck found that the sickling trait was transmitted both by the male and the female, the transmission apparently occurring according to Mendel's law for the inheritance of a single factor, the sickle cell condition being the dominant. The observations of Sydenstricker and his associates are in apparent agreement with those of Huck regarding the hereditary and the familial tendencies. Cooley and Lee, however, found that the transmission was through the mother. In a small series of cases, they did not find a single instance in which the father's blood was positive

for sickle cells and the mother's was negative, although the reverse was true. The last workers also concluded that the condition is "congenital, familial and hereditary," but failed to show evidence to substantiate the opinion that sickle cell anemia is a combined congenital and hereditary phenomenon. Sydenstricker observed sickle cells in the blood from the umbilical cord, as well as in the infants whose mothers had sickle-shaped red cells.

Cooley and Lee advanced an interesting hypothesis of a possible African tribe in which the sickle cell is the normal erythrocyte, but this theory is untenable if the finding of sickle cells in the blood of white people is true. That sickling is familial in the sense that it occurs in more than one member of the same family is concurred in by numerous writers on that subject. The sickling trait (sickle cell anemia) is generally accepted as being hereditary. The term hereditary is rather vague. Is it to be understood that the offspring inherits the constitution of either parent with the special defect that allows the formation of sickle cells or that some bacterium is present in the ovum or in the spermatozoon and is responsible for the sickle cell? Or are we to believe that bacteria or their toxic products either affect the ovum or the spermatozoon or pass through the placenta and act on the embryo? The inference drawn from the contributions of various authors is that the idea of an inheritance of a constitution with a special defect is the one that is understood. Huck amplified this view by maintaining that this inherited defect is a dominant character. It appears that the available data in the literature are insufficient for the absolute acceptance of the conception of the sickle cell as hereditary. In order to obviate an accidental coincidence observations on more than one family are necessary to establish Mendel's law for a given characteristic. If statistical data such as presence of a disease in parents and in their children are to be accepted as conclusively demonstrating an inheritance of a defective constitution, syphilis, if its etiology were unknown, could be explained on similar grounds.

Hahn and Gillespie in a series of ingenious experiments concluded that anoxemia is responsible for the formation of sickle-shaped forms in susceptible red blood cells. These investigators observed that on introduction of carbon dioxide, nitrous oxide and nitrogen into the medium containing susceptible erythrocytes the normal discoid forms assumed a crescent shape but when to this medium was added oxygen in a concentration of more than 6 per cent (a partial pressure of 45 mm of mercury) the sickle cells resumed their normal shape. As a corollary the authors hypothesized that the cause of the change of the susceptible red blood cell resides in the state of the hemoglobin when the hemoglobin is in a combined state the discoid erythrocyte is the result when it is in an uncombined state the elliptical cell is produced. They

also found that the pH changes of the medium (a decreased acidity resulted in an increase of sickle cells) apparently influenced the dissociation of oxyhemoglobin. These important observations demand further experimental corroboration.

Josephs believed that the changes in the surface tension of the cell and the serum with adsorption are responsible for the formation of sickle cells. This conception finds some indirect experimental verification in Hahn and Gillespie's experiments. When a surface of separation is present between a solid and a liquid, the molecules composing the surface are unable to move freely out of the plane and thereby acquire a resistance to rupture and an adaptability to a change of shape made possible by alterations in the interior of the solid. The surface tension of a liquid may be decreased by adding an acid, the protoplasmic gel of the solid will swell and change its contour. Hahn and Gillespie showed that an increased acidity of the medium resulted in the formation of sickle cells, a decreased acidity produced discoid erythrocytes. The last mentioned authors pointed out, however, that the change in the pH alone in the medium is insufficient to alter the shape of the cell. It may be assumed either that the gas also contributes to the change of the surface tension or that two factors operate: (1) an alteration of the surface tension and (2) the chemical state of the hemoglobin, as suggested by Hahn and Gillespie.

Emmel suggested that the sickle cell is produced by an accentuation of the normal hematogenetic activity which transforms a spherical erythrocyte into a biconcave disk.

Levy stated that the sickle-shaped erythrocyte is an embryonic normoblast that entered the circulation prematurely and is unable to assume the biconcave form. He based his belief on observations of extruded nuclei, a large number of normoblasts and the division of red cells in the same preparation in which are found sickle-shaped cells. Sydenstricker and Dreyfoos were of the opinion that there is some hereditary defect of the spleen and possibly of blood-forming organs which produces a change in the form of the erythrocyte. Hahn and Gillespie found sickle-shaped red cells several months after splenectomy had been performed (similar results reported by Stewart, Hahn, Bell, Kotte and their co-workers) and deduced from this that the spleen is not responsible for the sickle shape of red blood cells.

The bone-marrow and the general circulation are the two suggested sites of the formation of sickle cells. Sydenstricker believes that sickling occurs in the bone-marrow as a result of faulty erythropoiesis. Emmel, however, showed both in blood cultures and in direct smears various stages of transformation of disk-shaped erythrocytes into sickle shapes and therefore concluded that the change occurs in the circulation. Among others, Wollstein and Kreidel, on the other hand, observed

nucleated sickle cells in the bone-marrow. It is likely that whatever factors operate in changing the form of the red cell, these factors act equally on the erythrocyte in the circulation and in the marrow, and on the mature as well as the immature cell.

CHARACTERISTICS OF SICKLE-SHAPED ERYTHROCYTES

Emmel pointed out that if a culture preparation of the blood of a patient with sickle cell anemia or of a susceptible (sicklemic) person is allowed to stand at room temperature for several hours, most of the normal disk-shaped corpuscles become sickle shaped. These observations were verified by Huck, who noticed that in the blood of susceptible persons, 25 per cent of the normal erythrocytes, on standing for twenty-four hours, became bizarre or sickle-shaped. These observations were repeatedly confirmed by other investigators, and the phenomenon has been referred to as "latent sickling." Cooley and Lee stated that the rapidity of formation and the number of sickle cells in wet preparations have no relation to the presence or the absence of clinical manifestations, as suggested by Huck. Both Graham and Anderson drew attention to the inconstancy of sickle cell formation in wet smears. Smears prepared at the same time and under similar conditions showed either the presence or the absence of sickle forms. Huck found that if a blood culture preparation containing sickle cells was allowed to stand for from three days to six weeks, the cells resumed their spherical form. Levy, on the other hand, observed that sickle cells in wet preparations of blood from persons with sickle cell anemia failed to revert to the normal spherical biconcave disks. The reversal of the sickle cell to a biconcave or spherical form and vice versa was accomplished by Hahn and Gillespie by the introduction of various gases into blood preparations. The experiments of Hahn and Gillespie offer an explanation of the phenomena observed by Emmel and Huck.

The blood preparation usually employed consisted of a hollow slide with an inverted cover slip on which was placed a drop of blood, the cover glass was then rimmed with petrolatum. Such a preparation, probably by exclusion of oxygen, changed the biconcave disks to sickle forms. Hahn and Gillespie traced *in vitro* the various stages of the change from a biconcave disk to a sickle corpuscle. At first there was a change of refractivity of the erythroplasm, then a blotchy opacity appeared on one side of the rim and extended across the cell in radiating lines. This opaque blotch grew thicker, while the side opposite it became thinner, until it was hardly visible. The opaque side gradually showed a decrease in its curvature, while the thinned out side stretched from horn to horn to a half moon shape, the horns becoming longer and the thin side concave until a crescent was produced. In the light of this description, the

various forms observed by Emmel in stained smears and fresh blood preparations may be accepted as having been the stages in the transformation of a biconcave erythrocyte into a sickle one, and it suggests that sickling, for the greater part, occurs in the circulation.

Sydenstricker and his associates placed blood preparations containing sickle cells in the icebox and found no increase in the number of the sickle-shaped erythrocytes. On the other hand, similar preparations placed in the incubator resulted in a maximum number of sickle cells in four hours. The authors concluded that cold inhibits while heat accelerates the formation of sickle cells. Apparent contrary results were obtained by Cooley and Lee who placed a blood preparation containing sickle cells in the incubator (probably at 37 C) and found that the sickle erythrocytes had disappeared from the blood at the end of twelve hours. The last mentioned authors maintained that the absence of sickle cells was not due to a reversion to biconcave disks, but to a complete hemolysis. Levy confirmed Sydenstricker's observations that cold (0 C) inhibits the formation of sickle cells, and also expressed the belief that refrigeration acts as a fixative of red blood cells and prevents distortion of form. Levy also observed that incubator temperature (37 C) accelerated the formation of sickle cells, the change being complete in twenty-four hours. At the end of that time, the sickle erythrocytes began to fragment and many of the fragments were phagocytosed by leukocytes. The contradiction in the results obtained by the investigators in the time necessary for the complete reversion of the spherical cells to sickle cells (Sydenstricker four hours, Levy twenty-four hours, Cooley and Lee, complete disappearance of sickle cells in twelve hours) may lie in a difference in the conditions of the patients (sickleemia or sickle cell anemia) or a difference in the quantities of available oxygen in the preparations or some other difference in the experimental conditions. From these various experiments, it may be concluded that a high body temperature accelerates the formation of sickle cells, which are then destroyed by fragmentation.

Huck placed preparations of the red blood cells of people with sickleemia and sickle cell anemia in absolute darkness at room temperature. Sickle and bizarre shapes were formed just as quickly as in the control preparations exposed to the light, but reversion to spherical biconcave disks occurred with greater rapidity.

Josephs observed that susceptible erythrocytes washed and suspended in isotonic saline solutions retained or reverted to their normal spherical shape, but that when plasma or the third saline washings of red cells from normal or susceptible persons were added, sickle cells appeared. Graham and McCarty also failed to find sickling of centrifugated red blood cells which were placed in large volumes of buffered or unbuffered isotonic solutions. Josephs believed that the serum of any person con-

tains a substance which adsorbs on a susceptible erythrocyte and changes the shape to that of a sickle. This hypothetical substance, he believed, is washed off with saline solution. Josephs' observation that serum is essential for the occurrence of sickling is concurred in by Sydenstricker, Mulheim and Houseal. Huck, however, stated that sickling of red cells is not dependent on serum. He placed susceptible red blood cells washed in isotonic salt solution, in the serum of normal persons and that of persons with sickle cell anemia and found sickle and bizarre forms in the same proportions as in the control preparations. Since Huck did not examine the red cells after washing, but placed them immediately in serum, his results do not justify his conclusions in the light of Josephs' observations. Hahn repeated Josephs' experiments and found that the introduction of carbon dioxide into a preparation containing erythrocytes that had been washed in saline solution resulted in the production of sickle forms. He concluded that sickling of susceptible red blood cells is independent of any substance in serum. Experiments by different investigators conclusively established that normal red blood cells are not changed to sickle forms by serum from patients with sickle cell anemia, as suggested by Emmel.

When tissue of persons dying with sickle cell anemia was fixed in Zenker's fluid, no sickle red cells were apparent. However when formaldehyde was used as a fixative, sickle-shaped erythrocytes were found in large numbers (Graham). Hahn and Gillespie explained this phenomenon on the basis of the oxidation of Zenker's fluid. There is an increase in available oxygen and a consequent reversion of the sickle cells to the spherical form.

There are conflicting observations regarding the resistance of the sickle or susceptible red blood cells to various strengths of isotonic salt solutions. Some observers state that the resistance is normal (Sydenstricker, Alden, Cooley and Lee, Wollstein and Kierdel), others maintain that there is an increased resistance (Mason, Graham, Hahn, Landon and Lyman), while Huck found that there is a slight decrease. This contradiction may be due to a difference in the temperatures to which the preparations were exposed (Emmel, Huck, Cooley and Lee, Levy) and also probably to a difference in the condition of the patients. Mason was the only investigator to have made differential counts of the discoid and the sickle-shaped unhemolyzed red cells remaining in the tubes with the varying strengths of isotonic saline solutions to determine the difference in resistance between the sickle and the normal red cells.

Sydenstricker observed *in vitro* auto-agglutination of red blood cells from patients with sickle cell anemia. This phenomenon was corroborated by Josephs, who found agglutination in washed blood containing sickle cells. This tendency to agglutination was overcome only on

repeated washings of the blood preparation Hahn also noticed agglutinated red blood cells in sections of the spleen, and I have observed this phenomenon in the lung, kidney and spleen (unpublished)

The fate of the sickle-shaped erythrocyte in vitro under favorable conditions is a reversion to the normal biconcave form In the presence of adverse influences, the sickle cell is destroyed This destruction is carried on probably by more than one factor Emmel pointed out that sickle cells are phagocytosed by large mononuclears This observation was repeatedly confirmed by other investigators Both Sydenstricker and Lawrence noticed that polymorphonuclears perform a similar function In addition to the circulating cellular elements, the fixed tissue cells have also been implicated Jaffe Wollstein and Kreidel and others observed sickle erythrocytes within the Kupfer cells of the liver and it is probable that the reticulo-endothelial system as a whole acts in a manner similar to that of the large mononuclears and polymorphonuclears

Sydenstricker suggested that hemolysis plays a role The practically constant finding of biliary pigments in the blood of patients with sickle cell anemia he believed lends support to the conception On the basis of an extreme hemolytic activity evidenced by an extract of the spleen from a patient with sickle cell anemia, Sydenstricker intimated that the hemolysis is due to some substance secreted by the abnormal spleen In-vitro experiments of Levy indicate that fragmentation of sickle cells may occur with consequent phagocytosis of some fragments and possible hemolysis of others

The spleen as a hemoclastic organ undoubtedly plays a part in the destruction of red cells There is sufficient evidence to assume that the sickle erythrocyte is considered by the organism an abnormal cell and as such destroyed by the body defenses of which the spleen is a part

RELATIONSHIP OF SICKLE ERYTHROCYTES TO SICKLE CELL ANEMIA

A most plausible hypothesis advanced to explain the relationship between the sickle red blood cells and the severe anemia with the presence of similarly shaped erythrocytes is that of Hahn and Gillespie These authors suggested that the presence of a cardiac or pulmonary disease reduces the oxygen tension, and that as a result the red blood cells of susceptible persons assume the sickle form As pointed out, the sickle cells, being abnormal, are acted on by the phagocytic and the hemolytic body agents, with a consequent resultant anemia An almost constant observation at autopsies on persons with sickle cell anemia is an abnormal cardiac condition and less frequently some pulmonary disease The presence of heart and lung disease would support Hahn and Gillespie's view, if it were possible to exclude these conditions as results or manifestations of sickle cell anemia Dolgopol and

Stitt submit evidence contradictory to Hahn and Gillespie's view. Of seventy-seven tuberculous negroes, 52 per cent had sickleemia in contradistinction to 65 per cent of the nontuberculous negroes. Dolgopol and Stitt concluded that anoxemia caused by disease or compression of the lung is not an etiologic factor in the development of sickle cell anemia in sicklemic persons.

Cooley and Lee considered sickle cell anemia a form of familial hemolytic jaundice with a chronic hemolysis of vulnerable red blood cells by some hemolytic agent. In support of this opinion, it has been suggested that the spleen contains a hemolytic substance (Sydenstricker) which acts on sickle cells, but this conception fails to account for the transformation of the normal red blood cells to vulnerable sickle forms.

CONFUSION OF SICKLEMIA AND LATENT AND ACTIVE SICKLE CELL ANEMIA

A good deal of confusion is arising from the introduction of new terms by various authors. Cooley and Lee proposed for the phenomenon of the sickle cell trait the name of sicklemia, which is descriptive and simple. The terms drepanocytomia (Hahn and Gillespie) and mimosocytosis (Mason) are cumbersome and unnecessarily long. Latent sickle cell anemia, as suggested by Sydenstricker, has been erroneously applied to persons with the sickle cell trait, but the term as employed by its originator refers to an entirely different phase of the disease. Sicklemia (sickle cell trait) should be reserved only for those persons whose blood preparations on standing for from several to twenty-four hours show sickle erythrocytes, while the health of these persons is apparently normal, their blood without any other abnormalities and their previous history free of symptoms and signs of sickle cell anemia. Levy erroneously used the term sicklemia for the "symptom complex" that accompanies sickle red cells (Levy's cases included both active and latent sickle cell anemia).

Sickle cell anemia presents two phases depending on the degree of the clinical manifestations and the blood picture. One group of patients shows at the time of examination indefinite blood changes and only a few symptoms and physical signs, but gives a history which may include many or all of the manifestations of the so-called active sickle cell anemia. This group's blood preparations on standing reveal many sickle and bizarre forms. Sydenstricker applies to this phase of the disease the term "latent sickle cell anemia." Another group has marked and distinct clinical symptoms and signs and a definite blood picture. Sydenstricker suggested the name of "active sickle cell anemia" for the condition of this group. It has been observed that patients with an active sickle cell anemia have marked remissions with periods of comparatively good health and sudden recrudescences (Stewart). It is prob-

able that the latent phase represents merely the disease in a stage of remission

That sickle anemia and latent sickle anemia are two distinct phases is further corroborated by necropsies. Sicklemic persons (Cooley and Lee performed necropsies on four) show no pathologic changes suggestive of sickle cell anemia. On the other hand, Sydenstricker found in persons with latent sickle cell anemia dying from some other disease changes similar to, if not of the same degree as, those found in patients with the active form of the disease. Sydenstricker's observations at necropsies also support the idea that the latent phase is the stage of remission, the person dying of some other disease before repeated attacks of the anemia produced the marked changes characteristic of the active disease.

SICKLE CELL ANEMIA

Incidence, Race, Age Sex Symptoms and Signs—Cases of sickle cell anemia have been reported from widely separated localities in the eastern, western and southern parts of the United States. There was one case in Sudan (Aichibald), one in Cuba (Stewart) and a questionable case in Italy (Castana). Herrick's patient was a native of the West Indies.

Except for a few instances (the Greek family of Cooley and Lee, Stewart's Cuban child and Castana's patient with the questionable case), sickle cell anemia has been thus far found only in negroes or in those of negro blood.

The disease occurs frequently in children, but it has been observed in persons of all ages, the oldest patient being 78. Since sickle cell anemia probably affects only those with the sickle cell trait (sickle anemia), which is believed to be present at birth, the persons possessing this trait are probably exposed to repeated attacks of the disease from infancy. The condition, however, may not be diagnosed until adult life is reached and if the person afflicted survives the attacks, not until old age. Males are more frequently affected than females in the ratio of 3 to 1.

Most of the essential symptoms and signs of active sickle cell anemia were described by Herrick in his original communication. Herrick's patient had dyspnea, cough, palpitation, dizziness, chills, low fever, weakness, an ulcer of the leg, general adenopathy, yellow sclerae and a systolic murmur at the apex of the heart. Descriptions of other cases confirmed the presence of these signs and symptoms in a large number of the patients with sickle cell anemia. Additional manifestations reported by others consist of attacks of abdominal pains with nausea and vomiting, night sweats, headaches, pains of joints and muscles, enlargement of the liver and the spleen early in the disease, cardiac hypertrophy, an accentuation of the second pulmonic sound, a systolic

heart murmur heard best over the pulmonic area edema of the legs jaundice, swellings of joints and a comparatively low blood pressure (average of 105 systolic and 65 diastolic)

The latent phase of the disease manifests itself in pains of the muscles and joints attacks of abdominal pains, occasionally with vomiting weakness dyspnea green-yellow sclerae general adenopathy ulcer of the leg and enlargement of the liver and the spleen (Sydenstricker) It is apparent that the manifestations of Sydenstricker's latent phase vary only in degree from those of the so-called active stage of sickle cell anemia

Urine and Blood—The urine reveals frequently a low specific gravity (an average of 1.010) a small amount of albumin and varying amounts of urobilin hyalin and granular casts are often found and Graham reported a fixation of specific gravity The phenolsulphonphthalein output is not appreciably reduced (from 30 to 50 per cent in two hours)

The chemical constituents of the blood both organic and inorganic of persons with sickle cell anemia show little or no variations from the normal except for an increased bilirubin content and the almost constant presence of a positive indirect van den Bergh reaction In addition Graham and McCarty observed a variation in the blood cholesterol in different persons of from 208 to 877 mg per hundred cubic centimeters (by the method of Bloor)

The sedimentation rate of the red blood cells is increased (Graham and McCarty) The bleeding and the clotting time are normal The number of platelets is either normal or moderately increased (Graham Sydenstricker Huck Bell and co-workers and others)

The total number of leukocytes in the peripheral circulation varies in the same and in different persons but is practically constantly increased (from 11,000 to 64,000 per cubic millimeter of blood) The degree of leukocytosis apparently has no relation to the severity of the anemia or of the clinical condition The leukocytosis may be a manifestation of sickle cell anemia or of some intercurrent disease to which the anemia is believed to predispose the patient (Graham and McCarty) or it may be due to the primary cardiac or pulmonary disease (Hahn and Gillespie) on which the anemia is assumed to be engrafted Examination of the protocols of autopsies reveals that the associated disease in more than half of the cases may account for an increased number of leukocytes On the other hand a common observation in sickle cell anemia is a cellular hyperplasia of the bone-marrow It is more than probable that the leukocytosis is a manifestation of sickle cell anemia and not of an intercurrent or primary disease Except for a somewhat larger than usual absolute number of large mononuclear cells (Huck

observed 19.3 per cent in one case), the relative ratio of the constituent types of white blood cells is not disturbed. The relative number of the large mononuclear leukocytes does not seem to bear any relation to the degree of anemia. Occasionally, earlier forms of the granulocytic series (myeloblasts) are found in small numbers (from 1 to 7 per cent).

The amount of hemoglobin and the number of red blood cells in active sickle cell anemia vary, but are constantly moderately or greatly decreased. The relationship between the hemoglobin value and the erythrocyte count is also variable with a consequent shifting of the color index from below 1 (0.45) to 1 or over (1.4). The lowest hemoglobin content observed was 20 per cent (Bell and co-workers), the average being 44 per cent. The smallest number of red blood cells was found by Bell and his co-workers in their patient (976,000 per cubic millimeter), the approximate average is 2,100,000. In latent sickle cell anemia there may be either a normal or a slightly reduced amount of hemoglobin and number of erythrocytes.

In the active phase of the anemia, the abnormal morphology of the red blood cells is marked. There is a moderate grade of polychromatophilia, a marked anisocytosis with a large number of microcytes, fragmentary forms and a few macrocytes, an extensive bizarre poikilocytosis in addition to sickle and oat-shaped red blood cells (from 3 to 100 per cent in direct smear or in blood preparation after several hours), many embryonal forms, consisting mostly of normoblasts with a rare megaloblast, a reticulocyte count of from 10 to 40 per cent, and an occasional moderate punctate basophilia. In the latent stage of the disease, the abnormal morphology is slight or moderate. The direct smear reveals some polychromatophilia, a constant moderate anisocytosis of microcytes, some normoblasts, an increased reticulocyte count and poikilocytosis with sickle-shaped cells in a sealed preparation which has stood for from eighteen to twenty-four hours (Sydenstricker).

PATHOLOGY OF SICKLE CELL ANEMIA

The pathologic material on sickle cell anemia consists of sixteen more or less complete protocols of postmortem examinations. Of the sixteen patients, ten died of some intercurrent disease (three of tuberculosis, two of bronchopneumonia, two of peritonitis, one of meningeal hemorrhage, one of nephritis and one of pyelonephritis), which had no apparent relation to sickle cell anemia. In two other cases, the cause of death is not given, and the published records are too incomplete for one to arrive at a diagnosis. The postmortem protocols of the remaining four patients (one of Sydenstricker, Mulherin and Houseal and three of Wollstein and Kreidel) do not reveal pathologic changes of intercurrent diseases that may account for the deaths. Wollstein and Kreidel assumed that death in their three patients was due entirely to sickle cell

anemia Certain visceral alterations in the sixteen patients dying from different conditions were so constant that these changes may be considered peculiar to sickle cell anemia In the consideration of the spleen, additional data are available in the descriptions of the spleen removed at operation as a therapeutic measure

Ulcers of the Leg—Single or multiple ulcers of the leg were commonly present in the patients with sickle cell anemia The ulcers varied in diameter from 1.5 cm. to 7 cm., were oval but more frequently round, and shallow, had a punched out appearance, were slightly undermined and were indurated These ulcers persisted for a long period of time, but eventually healed with permanent scarring, they sometimes reappeared in the same or another part of the leg either spontaneously or following some trauma Microscopically, there was a moderate increase of connective tissue in the corium with a diffuse mononuclear (plasma, large mononuclear and some lymphoid cell) infiltration with a sprinkling of neutrophilic polymorphonuclears In places, blood vessels were surrounded by mononuclear cells The epithelium stopped abruptly at the edge of the ulcer The base consisted of granulation tissue (Huck) The scar was glossy, smooth and without pigment but was surrounded by pigmented skin

Heart—The heart was frequently hypertrophied, the hypertrophy being of a moderate degree and confined to the left side, predominately to the left ventricular wall (Hein, McCalla and Thorne, Sydensticker, Mulheim and Houseal, and others) No abnormalities of the pericardium or the endocardium either mural or valvular, were found, except in my patient in whom a chronic verrucose endocarditis of the mitral and aortic leaflets was present The myocardium, however, was frequently observed to have a slight to moderate patchy fatty degeneration (Wollstein and Kieidel, Graham, Hein, McCalla and Thorne) The myocardium of my patient showed a mononuclear infiltration and a patchy muscle necrosis Both the valvular and the myocardial lesions in my patient are considered to be of rheumatic origin In the absence of anatomic distortions of the valves, the heart murmurs noted by the clinicians must be assumed to have been functional

Lungs—Since no mention is made of any pathologic changes in the lungs in a comparatively large number of the protocols of the post-mortem examinations, it may be assumed either that the lungs were normal or that no examination of that organ was made Five of the patients had either bronchopneumonia or tuberculosis with pulmonary involvement, and whatever changes may have been due to sickle cell anemia were probably obscured Of the remaining patients there are five (including my patient), descriptions of whose lungs appear in the necropsy reports Marked congestion of the capillaries and the larger

vessels and the presence of serum in some alveoli were constant observations in all these lungs (the heart was of normal size in three of the five) When the tissue was fixed in formaldehyde many of the erythrocytes in the blood vessels were sickle shaped In my patient the small and the medium-sized pulmonary vessels contained fresh or organized blood thrombi with an occasional one canalized, and as a consequence there were fresh and old infarcts The cause of the thrombosis may have been either the abnormal and weakened myocardium or the tendency of the sickle-shaped red blood cells to agglutinate Wollstein and Kreidel described the observation in one of their patients of "wedge-shaped areas of organized pneumonia" and fibrous plugs in some of the alveoli

Spleen—The spleen was either enlarged or atrophied Wollstein and Kreidel correlated the size of the spleen with the age of the patient in a number of cases reported in the literature and found that the organ varied in size but enlarged with exacerbations of the anemia in the first four years of life, while in the older patients the spleen became smaller Stewart observed the size of the spleen at various intervals in a child from the age of 16 months to that of 5 years The first attack of sickle cell anemia was probably at the age of 10 months (patient reported to have been sick for 6 months) At the first examination the organ extended 5.5 cm below the costal margin, ten months later, it extended 6 cm below the costal margin, at the age of 4, the spleen was not palpable, and at 5 splenectomy was done and the organ was found to be reduced in size Stewart noticed that during a remission the spleen became smaller That the size of the spleen has no relation to the age of the patient per se is apparent from Sydenstricker's three "latent cases" in patients aged 78, 72 and 32 with spleens weighing respectively 460, 110 and 280 Gm It is probable that the severity and the frequency of the exacerbations are the responsible factors During the first attacks of sickle cell anemia the organ increases in size then with repeated attacks the spleen becomes atrophic

The spleen in the state of enlargement was reported (Landon and Lyman) in one instance to have attained a weight of 621 Gm (the patient was 4 years old) The enlarged organ was firm and frequently nodular, the cut surface was deep or purple red the follicles were diminished in size and the capsule and trabeculae were usually increased in thickness Histologically, the malpighian bodies were small, and the germinal centers were either absent or showed nuclear fragmentation Surrounding the follicles were areas of fibrous connective tissue or occasionally pools of blood The pulp and the sinuses were engorged with red blood cells the greater number of which were sickle shaped (formaldehyde fixation) The nodules apparent on the external surface

were due to dilated and engorged sinuses. Foot (in the case of Bell and his co-workers) observed a marked increase in the reticulin fibers, which were, however, absent near the malpighian bodies. Rich, on the other hand, did not find any abnormality in the reticulum. A brown pigment giving a positive reaction to the iron stain was found by some (Wollstein and Kieidel, Hahn and Gillespie) within endothelial leukocytes and in the thickened trabeculae. The pulp cells were diminished in number and were crowded by the masses of blood.

The smallest weight of the atrophic spleen was 2.4 Gm (my patient). The changes in the organ varied in degree with the extent of the atrophy. The external surface was frequently nodular. The cut surface varied from a dark purple to a brown-red, the follicles were small in the moderately atrophic spleen, and absent in advanced atrophy, the capsule and the trabeculae were thickened, there was a diminution in the amount of pulp with the presence of patches of connective tissue. The blood vessels were prominent, and the walls were thickened. Microscopically, the malpighian bodies either were not visible or consisted of a small nest of lymphoid cells without any germinal centers. Scattered throughout the organ were small accumulations of lymphocytes. The follicular remnants sometimes were surrounded by old or fresh hemorrhages or connective tissue. The capsule and the trabeculae were markedly thickened, and there were areas of connective tissue between the trabeculae. In the intertrabecular spaces there was a large amount of blood and brown pigment. The sinuses were always dilated, but sometimes were empty or contained from moderate to large masses of blood. The brown pigment within endothelial leukocytes in the pulp, in the trabeculae and in the vessel walls not infrequently gave a positive reaction to the iron stain. In a far advanced atrophy there was hyalinization and deposition of calcium in the arterial walls, in the thickened trabeculae and in the connective tissue. Although the splenic artery was never found thrombosed, the lumina of the small and the medium-size vessels were partly obliterated and occasionally contained thrombi. Foreign body cells with phagocytosed brown pigment were sometimes found.

Rich in a review of recent and old autopsies examined seventy-one spleens and stated that the histologic changes of the spleen in "latent and active" sickle cell anemia are sufficiently characteristic to establish a diagnosis of sickle cell anemia from an examination of that organ alone. Rich found an abnormal development of the follicular capillaries and a malformation of the sinuses around the follicles with presence of pools of blood in the pulp about the malpighian bodies. He believed that these abnormalities were congenital and were due to imperfections in the ampullae of Thoma. Hahn and Gillespie were of the opinion that the spleen injures itself when called on in its rôle of a hemoclastic organ,

to destroy an excessive number of erythrocytes. This splenic overfunction results in congestion, fibrosis and eventually atrophy of the spleen. Rich's observations are vague (no description of the abnormalities is given) and thus far remain unconfirmed. The changes he observed may have been results of splenic overfunction and not necessarily congenital.

Liver—The liver was consistently moderately enlarged. The architecture of the cut surface was blurred, and the color varied from red to brown. The organ was soft and friable, and in advanced cases of sickle cell anemia there was connective tissue in the central and paracentral lobular zones as well as an increase in the periportal connective tissue. Histologically, there was an infiltration of round cells in the periportal spaces and not infrequently in the liver lobules. The liver cells sometimes had a granular cytoplasm, and sometimes were atrophied or contained fat globules and a brown iron-containing pigment. The sinusoids were distended, filled with varying amounts of blood, and the lining endothelial cells frequently contained brown granules. The Kupffer cells were large and many contained erythrocytes and iron-bearing brown pigment.

Kidneys—The kidneys were of normal size or slightly larger. In the greater number of cases, the external surface was finely and irregularly scarred with an occasional large scar. The glomeruli were large and red. The cortical striations were frequently distinct and parallel. The medulla was yellow-green. Histologically there was an uneven capsular line due to numerous depressions (Sydenstricker, Mulherin and Houseal) and areas of radial scarring with partial or complete glomerular fibrosis and tubular atrophy (Graham). The glomeruli were prominent and the capillaries distended with blood. The tubular system, especially the loops of Henle, the convoluted and the collecting tubules, had large lumina frequently containing casts, the cytoplasm of the lining epithelial cells was granular and contained yellow or brown pigment (Graham and Wollstein and Kreidel demonstrated a positive iron reaction in the pigment, while Sydenstricker was unable to do so).

Bone and Marrow—Graham gave the most comprehensive description of the changes in the bone. He observed sclerosis of the cortex and the marrow cavity at both ends with a central red marrow beneath the ulcer of the leg. Elsewhere in the long bones (femur and tibia), the inner half of a generally thickened cortex contained islands of red hyperplastic marrow and areas of necrosis and intramembraneous bone repair. Practically similar changes were observed by Cooley, Witwer and Lee in the bones of the skull and the ribs. The last mentioned authors called attention to the porous appearance of the bones in roentgenograms early in the disease and a pronounced striation in the terminal

stages due to what they believed to be a replacement of the exhausted marrow by new bone. Practically throughout the cortex, Graham noticed lymphocytic foci and endothelial leukocytes with phagocytosed golden-yellow pigment, some of which was free in the form of threads. The marrow of the long and flat bones (Graham, Cooley, Witwer and Lee) consisted of a closely crowded mass of cells including myeloblasts, myelocytes, polymorphonuclears, many of which contained eosinophilic granules, a large number of nucleated red cells in the intercapillary spaces and a larger than normal number of megakaryocytes. Bizarre and sickle-shaped red cells both with and without nuclei were found by other observers (Sydenstricker, Wollstein and Kreidel, Mulherin and Houseal). The reticulo-endothelial cells (Graham) and the large mononuclears (Sydenstricker) contained pigment which varied from a golden yellow to a brown black. Sydenstricker was unable to demonstrate the presence of iron in this pigment, which he also found in intracellular form.

Other Organs—The mucosa of the stomach and the ileum contained a small number of neutrophilic polymorphonuclears, and the germinal centers of the Peyer's patches in the ileum had a few phagocytic endothelial leukocytes and polymorphonuclears (Graham).

The acinar and the "islet" cells of the pancreas contained a considerable amount of fat droplets. There was also a slight polymorphonuclear infiltration of the acinar epithelial cells (Graham).

The lymph nodes were frequently enlarged owing to a diffuse hyperplasia of the lymphoid cells. There were also some myeloblasts with neutrophilic and eosinophilic cytoplasmic granules, large mononuclears with phagocytosed pigment and a small number of polymorphonuclears in the sinuses and in the parenchyma.

No abnormal changes were observed in any of the other organs.

Bacteriology—Graham found a hemolytic streptococcus in the heart's blood, but the patient had a bronchopneumonia with an early empyema and apparently a similar organism was recovered from the lungs. Hahn and Gillespie isolated a green-producing streptococcus from the spleen of a 4 year old child who may have had some pulmonary disease (the authors described signs of impaired lung resonance, moist râles and a friction rub). Wollstein and Kreidel found a *Staphylococcus citreus* and a hemolytic streptococcus in the bronchial secretions of a patient who, however, had a "chronic pneumonia." I recovered from the bone marrow in my patient a pleomorphic gram-positive curved bacillus with the morphologic characteristics of a corynebacterium. The patient probably had a rheumatic lesion of the heart.

Since there is much probable evidence that points to the conception that some disease, possibly cardiac or pulmonary, when affecting a

person with the sickle cell trait, results in an exacerbation of sickle cell anemia, the bacteria found may be assumed to be associated with the intercurrent disease. Graham suggested that the streptococcus may be the responsible agent which acts on a person with an underlying sickle cell trait with a resulting production of sickle cell anemia. It may be also assumed that some micro-organism with a predilection for the bone-marrow produces a chronic inflammatory condition of the cortex (as described by Graham) and affects the marrow erythropoietic and leukopoietic activities and the morphologic appearance of the red cells. This micro-organism may be transmitted from the parent to the offspring and may have a greater pathogenicity for the colored than for the white race.

TREATMENT

Splenectomy, liver diet and blood transfusions are the three outstanding methods of treatment of sickle cell anemia. Sydenhacker suggested the removal of the spleen as a therapeutic measure, and Hahn and Gillespie performed the first splenectomy. Since then, Cooley, Bell, Landon and Lyman, Stewart and Hahn repeated this form of treatment in their cases. The spleens removed were of the atrophic and the enlarged type. In Hahn and Gillespie's patient, four weeks after splenectomy, the total number of red blood cells increased from 1,936,000 to 4,432,000, but the hemoglobin only showed a change of from 30 to 40 per cent. Both in Cooley's and in Bell's cases, there was an immediate rise in the number of red cells, but within six months after the removal of the spleen the hemoglobin and the red cells decreased to the preoperative level. The sickle-shaped cells persisted, and there was a marked increase in the number of the nucleated red blood cells. The white blood cell counts remained persistently high. Symptomatic improvement was reported (Hahn and Gillespie, Landon and Lyman). It is apparent that splenectomy is of questionable and at best only of temporary value in the treatment of sickle cell anemia.

Blood transfusions result in a temporary increase in the number of red blood cells and only in a slight elevation of the hemoglobin value. Cooley, Witwer and Lee found an excessive amount of iron excreted in the urine following transfusion and concluded that the donor's red blood cells were hemolyzed, although the recipient's serum failed to produce hemolysis *in vitro*. Following transfusion there was a marked increase in the number of normoblasts and megaloblasts, but the sickle forms persisted (Landon and Lyman). Similar to splenectomy, blood transfusions only temporarily decreased the anemia, and failed to stop the hemolytic process and had no effect on the formation of sickle-shaped red blood cells.

Levy fed liver to three patients with sickle cell anemia. In all of them he found an increase in the amount of hemoglobin and number of red blood cells, in one patient sickling of red cells disappeared, in the other two, the tendency to the formation of sickle cells was diminished. Levy's favorable report demands further corroboration by other investigators.

PROGNOSIS

Persons with the sickle cell trait (sicklelema) have lived to old age without any apparent disturbance in health. The prevailing conception is that sickle cell anemia per se is not fatal. There are only a few exceptions in which no other anatomic cause of death except the anemia was found (Sydenstricker, Wollstein and Kreidel). The patient with sickle cell anemia is subject to periods of indisposition, but recovery follows. It is believed that the disease in a child is more serious (Sydenstricker). The approximate average age in a number of cases collected from the literature at which the patient was first seen by the physician is 23. A patient with sickle cell anemia and some intercurrent disease is more apt to succumb to the secondary condition.

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THE FIRST TEXT OF PATHOLOGY PUBLISHED IN AMERICA

THE "TREATISE ON PATHOLOGICAL ANATOMY" BY WILLIAM
EDMONDS HORNER 1829 *

ESMOND R LONG, PH D, M D
CHICAGO

The year 1929, which commemorates the founding of the Chicago Pathological Society fifty years ago marks another anniversary in the history of American pathology, the centennial of the first textbook expressly devoted to pathologic anatomy in this country. The author was William Edmonds Horner, adjunct professor of anatomy in the University of Pennsylvania. It was published by Carey Lea and Carey, the publishers of the *American Journal of the Medical Sciences* in Philadelphia in the summer of 1829.

Horner was a native of Virginia born in Warrenton, June 3, 1793. Well written accounts of his life appear in the several standard works devoted to the biography of American physicians, and Middleton contributed an excellent character analysis to the *Annals of Medical History* (1923). As a boy, Horner was slender and delicate and he never came to enjoy robust health. He began the study of medicine at the age of 16, as an apprentice in the customary manner of the period. His preceptor was Dr. John Spence, a Scotch physician from Edinburgh, who had settled in Virginia, where he came into special prominence as one of the first and most forceful in introducing smallpox vaccination in this country. Spence was a pupil of the great Scottish physicians Cullen and Monro, and one who never swerved from the narrow path of Scottish medical doctrine. He died in 1829 the year of the publication of Horner's book on pathology, with which he must have had little sympathy, as I shall bring out later. Horner wrote an obituary, full of regard, in the *American Journal of the Medical Sciences*, of which they were both collaborating editors.

In the natural course of events, Horner went to the University of Pennsylvania to complete his medical studies. The relation of the Philadelphia school of medicine to the Edinburgh school has been well pictured by Dr. J. Gordon Wilson in his presidential address before

* Submitted for publication, Feb. 26, 1930.

From the Department of Pathology of the University of Chicago.

* Read at a joint meeting of the Chicago Institute of Medicine, the Chicago Pathological Society, and the Chicago Society of Medical History, Feb. 17, 1930, in commemoration of the fiftieth anniversary of the founding of the Chicago Pathological Society.

the Institute of Medicine. The leading teachers in the early period had all been graduates of the Scotch school. John Morgan, the founder, had trained with the Scotch William and John Hunter in London and gone to Edinburgh to graduate. William Shippen, Jr., the first teacher of anatomy, had done likewise. Benjamin Rush graduated in Edinburgh after training with Shippen. In Horner's time the Edinburgh graduates were still in the major positions. Even had Philadelphia not been convenient in location, the Scotch John Spence would certainly have directed Horner there for didactic work to supplement the practical office and bedside experience of a physician's apprenticeship in a small Virginia city.

Horner's first studies in Philadelphia were cut short by the war of 1812. He entered the army as a surgeon's mate in July, 1813, at the age of 20, and saw much active experience on the Niagara frontier, which he described years later in a series of interesting articles, extracted from his diary.

During a furlough in the winter of 1813-1814, he returned to Philadelphia and graduated, using his recent experience for a thesis on gunshot wounds. Following his discharge from the army, he practiced medicine for a short time in his native town of Warrenton, but after a few months made up his mind to return to Philadelphia. From the outset of his medical training, he had been most strongly attracted to the study of the structure of the human body. In 1815 and 1816 he attended lectures in this subject, where his zeal came to the notice of the great Philadelphia anatomist Caspar Wistar, professor of anatomy. In March, 1816, Wistar offered Horner the position of dissector at \$500. Horner's fortunes were henceforth identified with the department of anatomy in the University of Philadelphia. On Wistar's death in 1818, John Syng Dorsey became professor of anatomy and Horner rose to the position of demonstrator. Dorsey died a few months later, and his uncle, the distinguished Philip Syng Physick, left the position of professor of surgery to assume the chair of anatomy. Horner was promoted again, to the position of adjunct professor (1820), shortly afterward he became dean of medical school, and eleven years later he succeeded Physick as professor of anatomy, himself.

During this time, Horner also acquired a private practice in the city. It is interesting to note that in his early days, before he had quite settled down to an academic life, he had wished to accept a position as ship surgeon in an East Indiaman. The longing to travel proved almost too strong a temptation. He refused only because his feeling of moral obligation to his chief, Caspar Wistar, was stronger. A deeply pious person, constantly subjecting his own private thoughts to the sternest

critical examination, he entered this note in his journal in 1816 "My refusal was the result of my sense of obligation and honorable intentions with regard to Dr. Wistar. It is said that honesty is the best policy here, then is a trial of the rule." Years later, on Jan. 1, 1832, he subjoined to this entry the naively triumphant addition, "See note of Trustees of the University of Pennsylvania appointing me Professor of Anatomy *vice* Dr. Physick, resigned." He had just succeeded to the first chair in anatomy, one of the outstanding positions in the teaching of medicine in the country.

In the intervening years he had married, acquired a good financial competence, traveled abroad and done most of his best work. The



WILLIAM EDMONDS HORNER
1793-1853

distinguished surgeon and American medical historian Samuel Gross spoke of him several decades later as the most accomplished anatomist that this country had produced. Horner had recited Wistar's "Anatomy" (1823), published a "United States Dissector or Lessons in Practical Anatomy," which was to go through four editions, and put forth a monumental "Treatise on the Special Anatomy of the Human Body" (1826) of which ultimately eight editions appeared. He had written a short article, which has preserved his name in anatomic nomenclature on a muscle of the orbit now known as the "tensor tarsi" or "Horner's muscle." He had published numerous articles of import for pathology in the *American Journal of the Medical Sciences* and written the text in this subject in 1829 which is the subject of this paper.

The origins of this book may be traced to several sources. The motive of publication was given by Horner himself in the Preface:

The following work is intended more especially for the use and guidance of practitioners of medicine. It treats of a department in our science comparatively strange to the mass of medical men and for which there is no sufficient provision by the plan of instruction in any of the numerous colleges of our country. Pathological anatomy by the recent organization of the most improved schools of Europe has taken a high and commanding attitude. The numerous observations which have been made in it and the increased skill arising from various and accumulating experience have at length enabled its cultivators to systematize its facts and to make a close and instructive application of them to nearly every case of disease, which they are called upon to treat. It is now almost universally conceded to be the light and test of every opinion in medicine and when the latter fails to harmonize with it whatever may be the ingenuity of the opinion it is not likely to obtain either permanent attention or consideration and must perish in that oblivion which has buried so many medical theories. The modern pathologist has ceased to consider disease as an independent existence which may insinuate itself into the human body and whenever its name is mentioned he invariably associates with it the existence of a change or lesion in the structure of some part of the body, which in fact, is the disease itself.

It was indeed lamentably true that pathology was a science comparatively strange to American physicians and unprovided for in university medical instruction. This was at least in part the fault of the very school of medical thought responsible for the high position of the medical department of the University of Pennsylvania i.e. the set of doctrines originating in Edinburgh. The speculative pathology of the Scotch physician John Brown good enough for Benjamin Rush was still dominant and only beginning to give place to the new learning on pathologic anatomy coming from Paris. Philadelphia physicians groping in their own experience for this new light turned to the anatomists for help. Horner made many postmortem examinations at their request in cases that had been found puzzling. He took the professional ethics of this relationship most seriously as may be seen from the following earnest expression of his views on the obligations involved (from the preface of the 'Treatise on Pathological Anatomy').

I know in fact no higher mark of the confidence which one physician reposes professionally in another than an examination subsequent to treatment: the errors and misconceptions of the prescriber are there fully exposed when they have occurred and his reputation stands more or less committed. Happily for our profession breaches of confidence on this point are very uncommon in my own personal observation I have never known of one and such a betrayer would be justly held in so great abhorrence that his first treachery would also be his last.

Horner knew that the science of medicine would inevitably extend to its practice and he saw pathologic anatomy destined to become the basis of scientific medicine. His European trip of 1821 must have opened

his eyes to this certainty. All his later writings indicate that French pathology, as developed by Bichat and his successors of the following generation, made a profound impression on him. His new views, however, marked a great departure from his original teaching at the hands of John Spence and the Edinburgh trained masters in Philadelphia.

TREATISE

ON

PATHOLOGICAL ANATOMY.

BY

WILLIAM E. HORNER, M. D.

ADJUNCT PROFESSOR OF ANATOMY IN THE UNIVERSITY OF PENNSYLVANIA,
 SURGEON AT THE INFIRMARY OF THE PHILADELPHIA ALMS HOUSE,
 MEMBER OF THE AMERICAN PHILOSOPHICAL SOCIETY, &c

PHILADELPHIA.

CAREY, LEA & CAREY—CHESNUT STREET.

1829.

Fig. 2—Title page of Horner's "Treatise on Pathological Anatomy."

The strong feelings of Spence cropped out in a letter which Horner cited in writing his old teacher's obituary. The recipient of this letter is not named, but was presumably Horner himself. The obituary reads:

Our colleague (that is, Spence) was much attached to the theories and modes of practice in which he had been educated. Having imbibed his first principles in the school of Cullen and under his immediate teaching, they never were obliterated.

ated from his mind, and were to him the infallible evidences and tests of medical soundness and truth. In a letter to a correspondent of a recent date, he says "Your devotedness to French pathology may lead you into error, you may thereby run the risk of the young advocate of Brown's system, that of a charge of servility and the want of original eclectic power. I fear the consequences of the present rage for this ultra French pathology, which seems to rest almost everything on a hypothetical basis. In these remarks I confine myself to the doctrine of idiopathic fever—of gastro-enteritis.

"When John Brown published his *Elementae Medicinæ*, referring all diseases to tonic and atonic he observed that the bilious remittent fever of hot climates was a disease of debility and must be treated at once by stimulants. In the second edition of his *Elementae*, he says in a note that he must correct his former prescription, for that some of his young American friends and pupils (and the American students were devoted to him) informed him that without previous evacuations from the stomach and bowels, his stimuli would destroy such patients—and he followed their advice. Can you suppose that old practitioners like myself would surrender a long-trying and successful practice in bilious fevers for this novel system of Broussais—no—never. But I cannot bring myself to believe that you embrace the ultra French pathology to the exclusion of prescriptions sanctioned by men of intelligence, observation, and nice discrimination. If you did I would say

"Incedis per ignes
Suppositos cineri doloso"

'I agree with you that such lectures (meaning lectures on pathology) should be incorporated into your plan of public education, and rendered essential to obtaining a diploma.

"The success of your University has caused much dissatisfaction and envy—and now they wish to injure its fame, by giving out that the ultra pathology of France, is the ruling passion of your professors."

The mortality statistics collected in 1829 for the preceding year in Philadelphia throw sufficient light on the lack of anatomic localization of disease in America at this time. The ten chief listed causes of death were (out of 7,033 deaths) consumption, 581, stillbirth, 321, convulsions, 315, cholera, 291, debility, 286, inflammation of the lungs, 130, dropsy in the head, 110, fever, 118, smallpox, 107 and bilious fever, 105.

Also listed in this imperishable record were atrophy, 38, decay, 16, old age, 64, cancer, 18, casualties, 19, sudden, 55, found dead, 29, mania a potu, 82, drinking cold water, 5, hives, 71, teething, 7 and unknown, 71.

Attention in passing should be called to the item cholera. This was fearfully prevalent at the time, and Horner himself in succeeding years did much toward its control, his investigations including an abundant experience in the postmortem examination of this disease. After the epidemic of 1832, the City of Philadelphia presented him with a magnificent inscribed silver pitcher in recognition of his services.

Horner's "Treatise on Pathological Anatomy" was by intention and in effect an entering wedge for improvement in the situation revealed

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by these figures. As a teacher of young men who were to become physicians, and as a prosector for fellow physicians, he felt the need of an American textbook in the subject. He had already published a number of articles which he felt might well be incorporated in such a book. He had for several years been particularly interested in modifications in the appearance and texture of the gastro-intestinal tract. One can see here the influence of Broussais, who had made a profound impression on Horner in Paris in 1821. The latter, to his credit, however, never pushed Broussais' doctrines of gastro-enteritis to the absurd extremes of the famous French clinician. The *American Journal of the Medical Sciences* opened in 1827 (it had been previously published under another name) with an article by Horner, who was one of the thirty-nine collaborating editors of the new journal, entitled, "Inquiries into the Healthy and Diseased Appearance of the Mucous Membrane of the Stomach and Intestines." Colored plates were appended. This article and a later one entitled "An Inquiry into the Anatomical Character of Infantile Follicular Inflammation of the Gastro-Intestinal Mucous Membrane, and Its Probable Identity with Cholera Infantum" (1829), were copied with a few additions but otherwise practically verbatim into the "Treatise on Pathological Anatomy" as chapters 10 and 11.

A detailed analysis of the chapters of this book would be unnecessarily tedious. For the purposes of this review, it may be divided into three parts although it is not so divided in the organization of the work. The first of these might be entitled General Pathology, the second deals with Horner's own contributions and views in specific fields, and the third is devoted to a summary of the pathologic doctrines of other investigators in respect to some of the most important portions of the subject. These are almost without exception French. The views quoted are taken directly from the famous writings of Bichat, Corvisart, Laennec, Louis, Andral and others, with abundant quotations from French works like those of Gendrin and Roche and Sanson, which have long since been forgotten. Horner's information on the heart is Corvisart's, his picture of diseases of the chest is Laennec's, his knowledge of diseases of the central nervous system comes from Lallemand, and so forth. It is true that in most instances he could not have done better, and the greatest strength of the book rests in the weight derived from these foreign authorities. His summary of their views is abundantly supplemented from his own post-mortem experience chiefly from his service in the infirmary of the Philadelphia Almshouse. Eighty-nine partial or complete records of necropsies from Horner's experience appear in the book.

It must be confessed at once that as an independent pathologic anatomist Horner was deficient. He was an excellent normal anato-

mist, extremely well versed in the exactitudes of that science, but in the deductions and subjective evaluation of tissue changes, which are basic to pathology, he fell short. His protocols of necropsies are, for the most part, purely descriptive, and do not achieve their object of clinical explanation. His picture of inflammation of the gastro-intestinal tract is largely erroneous. Indeed one may perhaps hold Horner partly responsible for the familiar fallacy of naming acute gastritis as a cause of sudden death, still all too common in coroner's records. Although he recognized "active and passive congestion" of capillary beds, and was familiar with John Hunter's work on postmortem digestion of the stomach, he designated as inflammation what appear to have been simple postmortem settlements of blood in the wall of the bowel, and wrote voluminously on mollescence of the stomach. He attached a great deal of significance to the common punctate extravasations of blood in the gastric mucosa, and took for manifestations of primary disease what we now recognize as simply the necessary anatomic results of the vastly overenergetic purgings and bleedings and starvings of the current medical practice. It is interesting to note that in a brief history of pathologic anatomy with which Horner prefaced his treatise on the subject he criticized in an able manner such writers as Bartholin, Bonet and Morgagni for the errors into which he later fell himself. Nevertheless his necropsy experience covered an enormous range in pathologic anatomy and must have made Horner and the physicians whom he assisted familiar with the gross appearance of carcinomas of the esophagus stomach and rectum tuberculosis of the lungs larynx and pericardium, pleural and peritoneal effusions, aneurysm of the aorta calcification of the aortic valve pericarditis and many more common lesions, and his book unquestionably went far to spread this knowledge in a profession whose members had very rarely gone further in post-mortem experience than routine dissection for instruction in normal anatomy.

The first nine chapters of the book deal with the principles and organization of pathology. Although the classifications of lesions proposed is a borrowed one, critical examination of this reveals a good deal of self determination in the analysis of types of lesion. The classification is the clumsy one favored in continental Europe in this period stressing abnormalities from a mechanical point of view. Horner at the outset proposed to limit his discussion to the first of thirteen types of lesion viz irritation. This in turn, is divided into six subtypes inflammation (or phlegmasia), hemorrhage subinflammation neurosis, nutritive irritation and secretory irritation.

Attention may profitably be confined to Horner's views on the first of these. Inflammation is the keystone of pathology and it is probably

sound to evaluate any set of doctrines in the science by the character of the consideration devoted to this phenomenon

Horner himself counted acute inflammation as the beginning of 90 per cent of disease. He cited its four classical manifestations, but rightly directed attention to the fact that these are seen typically only in inflammations of the cellular i.e., subcutaneous connective tissue and are not necessarily characteristic of inflammation elsewhere. He said "Pathologists have been led into the error of adopting the type of inflammation in it (cellular tissue) as the type of inflammation in other parts. They have stumbled and fallen at the threshold of their inquiries by expecting identical phenomena in all other tissues, even in those least resembling it in composition and mechanical arrangement.

In a brief and accurate fashion well suited to didactic teaching, Horner listed the several ways in which inflammation may subside. Few references are cited. His generalizations appear to come from both reading and observation. His treatment of the subject is almost entirely descriptive, however, and in striking contrast to the lengthy teleologic approach of another work which at once comes to mind that of John Hunter, who saw design in every one of the phenomena of inflammation.

Horner was certainly familiar with Hunter's masterpiece with the blood-curdling title "Blood, Inflammation and Gun Shot Wounds," which was widely read in this period. It might be supposed that the truly spiritual view of the phenomena of inflammation taken by Hunter would have appealed strongly to Horner, by nature a devout conformer to religious convention. But Horner must have considered this aspect of Hunter's treatment of the subject impractical in a textbook for practitioners. He had nothing to say of the beneficent principles underlying the manifestations of inflammation which seems to have appeared to him a wholly malignant process, indeed as the cause of disease itself, and not as a reaction to a still prior inciting agent. Horner's insistence on a simple descriptive treatment of inflammation, and his failure to take a physiologic view of the subject, make his initial chapters dull reading. He could not foresee, of course, the cellular pathology and bacteriology of today, and the present frankly vitalistic immunology with its antibodies, phagocytes etc. But a rich physiologic background for views on inflammation was available to him, of which he took no advantage. In this respect, the highly accurate descriptive French pathology, which had seemed to him such a torch in the current lack of illumination on the nature of disease held him back.

It would be interesting to know a little more of the reception of Horner's book in his own time. It was reviewed by John Godman in the *American Journal of the Medical Sciences*, but the review is devoted largely to Horner's eminent qualifications for writing such a book and scarcely at all to the merits of the book itself. Ten years

after the publication of Horner's work, a far better treatise on the subject appeared in Samuel Gross's "Elements of Pathological Anatomy," which became immediately the standard American text.

To form a just view of Horner's book, one should compare it with those appearing elsewhere at approximately the same time. It suffers in the comparison. It was published in the same year as the two volumes on typhoid fever by Louis of Paris. The latter was by far the abler product. Richard Bright's "Report of Medical Cases," with its classic account of nephritis, had been out a little less than two years. Horner gave no indication of having seen or profited by this far more inspiring compilation. Cruveilhier's "Pathological Anatomy of the Human Body" was in preparation, and on publication proved to be the product of a much superior hand.

Nevertheless, with all its defects, the "Treatise on Pathological Anatomy" was a courageous piece of pioneering, wholly in accord with America's frontier traditions. Horner, one of the humblest of his profession in the estimation of his own capacity, seeing a fundamental weakness in American medicine, and nobody to improve the situation but himself, quietly assumed the responsibility. For ten years his product stopped the gap, and in that time must have been a constant stimulus toward a pathologic-anatomic point of view in American practitioners of medicine, if not toward an exact interpretation of all the symptoms of illnesses encountered or an understanding of all the lesions seen.

Horner lived twenty-four years after the publication of his "Treatise on Pathological Anatomy," devoting the major share of his literary energy henceforth to the elucidation of normal structure. During these years his health became steadily worse, and his temperament more melancholy. Migraine headaches and fits of indigestion, which had distressed him since childhood, increased in severity. How his physical condition affected his working capacity only Horner himself knew, as he gave little outward sign of his trouble. But he did once complain that "a man who suffers from pain in the head during three-fourths of his waking existence cannot be expected to perform much work without great discomfort and dissatisfaction." He grew more introspective and self-deprecating. He spent hours in prayer, in the morbid feeling that he must be undergoing punishment for his sins. To the best of his remembrance, he had always walked faithfully in the sight of men, but had he done so, he repeatedly asked his inmost self, in the sight of God? In 1839, he joined the Roman Catholic Church. It was no sudden resolve, but the result of years of pondering, and partly the aftermath of his experiences in the cholera epidemics of Philadelphia, where time after time he had seen Catholic priests and sisters, with the characteristic self-effacement of their creed, alone standing at their posts in the universal panic inspired by this fulminating disease.

He continued his teaching to the end of his life. Never a fluent teacher, he was always an accurate one. His own anatomic preparations were faultless and he tolerated no carelessness in his assistants. His lectures must have been monotonous, but through insistent repetition he drove his lessons home. A gradual failure of the heart, with increasing dyspnea, added to his disability in his declining years. In the last year of his life, he used to appear before his classes with edematous legs bandaged almost to the hips. The death of a beloved daughter in 1852 broke the morale of this faithful laborer, beyond recovery. Even from his bed, however, he continued to attend to the needs of his students, and three days before death assisted in an examination. An acute abdominal attack hastened his end, a terminal peritonitis carrying him off on March 13, 1853, a broken, atherosclerotic old man, whose heart had long been decompensated and who had aged years before his time.¹

His services to anatomy have gradually been forgotten, except as commemorated in the relatively insignificant "Horner's muscle." The great contributions to medical education by this man, who was for over thirty years dean of the first and in its time foremost medical school, are scarcely recalled. Still less is it now remembered that it was he who truly introduced modern pathology to his profession in America, by example if not by innate capacity. In his impressionable twenties he had been remolded in the training of the great French school of pathology, and, practically alone in his own country, he set out to impregnate American medicine with the new learning, the epitomized expression of which by a leader of that school (Jean Cruveilhier) is set down in the preface of his treatise. A physician without pathologic anatomy could, indeed, be ever so skilful in practice, but although he might see many patients, he would see no diseases.

1 The following account of his final illness was given by Dr. Samuel Jackson on Oct. 10, 1853, in an address to the faculty and students of the University of Pennsylvania ("A Discourse Commemorative of the Late William E. Horner, M.D." Published by the Class).

"It is somewhat remarkable that the death of Doctor Horner was not the immediate result of the chronic affection under which his constitution had broken down. He had complained about the 10th of March of pain in the abdomen on the left side. On the night of the 12th it suddenly assumed an intensity that led to the suspicion of peritonitis from a perforation. He sank exhausted by unceasing and unmitigable suffering the evening of the next day, March 12, surrounded by his sorrowing family and relatives.

"Examination after death revealed the existence of entero-peritonitis, with mortification of the small intestines. This new condition was the direct cause of death, and had suddenly supervened on the original disease."

Speculation on the cause of this peritonitis is enticing, but in the lack of a more thorough clinical and postmortem record would be equally uncertain.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths—

On his eightieth birthday, April 8, William H. Welch, professor of the history of medicine, Johns Hopkins University, was honored by simultaneous celebrations in London, Paris, Berlin, Leipzig, Tokyo, Peiping, Baltimore, Cincinnati, New Haven, New York and Washington, D. C. At the Washington ceremonies, addresses were made by President Hoover and Simon Flexner, with a response by Dr. Welch.

Andrea Saccone has been appointed assistant professor of pathology in the New York Homeopathic Medical College.

A memorial meeting in honor of Richard Mills Pearce, Jr., was held April 15, 1930, at the Rockefeller Institute for Medical Research, New York, at which addresses were made by George E. Vincent, David L. Edsall, Howard T. Karsner and Simon Flexner.

The Academy of Medicine of Cleveland has conferred honorary membership on George Neil Stewart, director of the Cushing Laboratory of Experimental Medicine at Western Reserve University.

On retiring from the U. S. Army, May 1, Lt. Col. Fielding H. Garrison, medical historian and assistant librarian in the Army Medical Library, Washington, D. C., from 1889 to 1922, will assume the duties of librarian of the Welch Medical Library, Johns Hopkins University.

Herbert M. Evans, professor of anatomy in the University of California, has received an honorary doctorate from the medical faculty of the University of Freiburg, in recognition "of his conspicuous anatomic and biologic discoveries, especially in the sphere of vitamin research."

Karl Landsteiner, a member of the Rockefeller Institute for Medical Research, New York, was awarded on March 14, the anniversary of Ehrlich's birth, the Paul Ehrlich gold medal of the Paul Ehrlich Foundation of Frankfurt-on-the-Main, in recognition of his work on human blood groups and his haptin theory of immunity.

The resignation is announced of Roger Griswold Perkins, professor of bacteriology and preventive medicine and head of the department of bacteriology and hygiene of the School of Medicine of Western Reserve University. Dr. Perkins desires to be liberated from university duties so that he may have more time for special studies. He will live at Wakefield, R. I.

Congress of the International Society for Microbiology—The date of the first congress, which is to convene in Paris, has been changed again, this time to July 20 to 25, 1930.

American Society for Experimental Pathology—At its recent meeting in Chicago, the following officers were elected for the ensuing year: president, Frederick L. Gates, vice-president, Samuel R. Haythorn, secretary-treasurer, C. Philip Miller, Jr., and councilors, Peyton Rous and Carl V. Weller.

Prize for the Study of Goiter—Beginning this year the American Association for the Study of Goiter will award a cash prize of \$300 annually for the best original thesis dealing with some phase of the goiter problem. Theses should be submitted by June 1 to Dr. Walter M. Simpson, Chairman of the Essay Committee, Miami Valley Hospital, Dayton, Ohio. The award will be given immediately following the coming meeting of the association which is to be held in Seattle, July 10 to 12, 1930.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EXPERIMENTAL PRODUCTION OF ABSCESS OF THE LUNG ELLIOTT C CUTLER, *Am J Dis Child* **38** 683, 1929

The surest way to produce an experimental pulmonary abscess is by the use of an infected embolus. No abscess is formed following aspiration and insufflation of infected material into the air passages unless there is complete bronchial obstruction with subsequent atelectasis and anaerobiasis. It is suggested that an embolus from a septic field causes the original lesion and that this becomes a chronic abscess only by being secondarily infected by aspiration of organisms from the mouth and upper respiratory tract.

J N PATTERSON

DIETARY CONTROL OF DENTAL CARIES J D BOYD, C L DRAIN and M V NELSON, *Am J Dis Child* **38** 721, 1929

Dental caries has been arrested in many instances under divergent conditions of health and environment, by the ingestion of diets high in mineral and vitamin content. All diets were designed to give adequate proteins and calories, but in other respects they varied widely. The arrest usually becomes apparent after about two months of dietary control. On the basis of the clinical and experimental observations, it is thought that active caries should be viewed as indicative of nutritional deficiencies. These deficiencies may not make themselves obviously apparent in any other way. Yet when the food intake is made adequate, caries will become arrested, and in other respects there will be evidences of better health.

AUTHORS' SUMMARY

DIFFERENCES BETWEEN HIGH AND LOW INTESTINAL OBSTRUCTION IN THE DOG J J MORTON, *Arch Surg* **18** 1119, 1929

In his preamble concerning the mechanism and etiology of the toxemia of intestinal obstruction, the author concludes that the role of bacteria has not been excluded. His investigation is concerned with anatomic and physiologic differences between the duodenum and the ileum, the object being to show that there is an anatomic explanation for the more rapidly developing toxemia in high obstruction as compared with low obstruction. The vascular supply and capillary bed were injected in equally measured segments of the lower duodenum and terminal ileum. This showed that the arterial supply and the capillary network were much greater in the duodenum than in the ileum. By a similar method of injection, he was able to demonstrate that the duodenal villi were thicker and much more closely placed than in the ileum. The ability of the duodenum to withstand intraduodenal pressure seemed to be somewhat greater than that of the ileum. The musculature in the duodenum was about one-third again as great as that of the ileum and the wall was thicker. The secretory powers of the two portions were compared in obstructed loops, and it was found that the duodenum secreted anywhere from five to ten times as much fluid as the comparative loop of the ileum. This in itself would produce a great pressure in the duodenum and outweighs the resistance of the duodenum to pressure, hence necrosis and perforation always occurred in the duodenal loop before they did in the loop of ileum. The mechanism which caused the more rapidly developing toxemia may be explained by the intraduodenal pressure squeezing the toxins through the wall into the circulation. The latent period in which there are no symptoms is taken up by the secretion of fluid and bacterial growth. Then the absorption of histamine and histamine-like bodies and the

products of bacterial growth occurs, and with it the engorgement and edema and peculiar dusky cyanosis of the wall develops. Nevertheless, no conclusions could be drawn from his investigations on the exact pathway by which the toxins are absorbed

N ENZER

EXPERIMENTAL DIABETES INSIPIDUS E B TOWNE, Arch Surg **18** 1165, 1929

An attempt was made to produce diabetes insipidus in dogs by dividing the stalk of the pituitary high enough up so that all epithelial cells of the pituitary gland would be detached from the base of the brain. Ten dogs were operated on, and six survived. Polyuria lasted from four to twenty-one weeks. At post-mortem examination, serial section of the hypophysis and base of the brain showed that the division of the stalk had been high enough to detach all cells of the pars tuberalis in only one of the dogs. In the others small groups of cells had been left attached to the under aspect of the third ventricle. Nevertheless, a permanent polyuria did not develop. The finding of eosinophilic cells in the nest of epithelial cells found at the base of the brain was interesting. Also, a few similar cells were found in the pars intermedia and pars tuberalis which had become reattached to the uninjured base of the brain in one dog. The author discusses the various theories concerning the rôle of the pituitary and the base of the brain in diabetes insipidus, and from his experimental work could not draw any definite conclusions. The important thing is that the pars tuberalis cannot be dismissed as having no influence, and it does seem that from his experiments the neurogenic origin of this syndrome can be disproved, since the polyuria ceased when the pars intermedia became reattached.

N ENZER

SEPARATION OF GROWTH-PROMOTING HORMONE FROM THAT INDUCING PREMATURE ESTRUS IN THE ANTERIOR PITUITARY GLAND T J PUTNAM, Arch Surg **18** 1699, 1929

This work is chiefly concerned with the repetition of the experiments of Evans and Long (*Anat Rec* **21** 62, 1921). It was found that by using an alkaline extract of the anterior pituitary on dogs a condition of acromegaly was produced. These dogs increased in weight and developed enlargement of the acro parts, polyphagia, asthenia, sialorrhea and spontaneous lactation. Estrus did not develop. Autopsy showed skeletal overgrowth, splanchnomegaly, hyperplasia of the thyroid, adenomas of the suprarenal glands, enlargement of the uterus and vagina and cysts in the ovaries, but no lutein tissue. The transplantation of fresh and old anterior lobe material in rats resulted in premature estrus, but did not produce it in animals that had been spayed. Putnam failed to demonstrate glycosuria in hypophysectomized rats in anterior hypophysectomy. In discussing the possibility of more than one hormone being present in the anterior pituitary, there seems to be evidence that an alkaline aqueous extract brings about different results from those following the implantation of the insoluble residue. The latter produces premature estrus, whereas the former causes growth of the mesodermal tissues.

N ENZER

STUDIES IN ACROMEGALY T J PUTNAM, E B BENEDICT and H M TEEL, Arch Surg **18** 1708, 1929

This article is concerned largely with a detailed autopsy description of a dog that received a daily injection of an aqueous extract of the anterior lobe of beef hypophysis for fourteen months. It grew to twice the weight of its control. At autopsy, it presented all the physiologic and skeletal changes of acromegaly. The hyperplastic change in the thyroid was more striking than that seen in human material, and also the unusual enlargement of the uterus and vagina. It is possible that the extract used here contained an estrus-producing hormone isolated by Evans and Simpson.

N ENZER

CEREBROSPINAL FLUID CHANGES IN COMPOSITION AND DRAINAGE AFTER
INTRAVENOUS ADMINISTRATION OF VARIOUS SOLUTIONS R G SPURLING,
Arch Surg **18** 1763, 1929

A freely draining cisterna magna was produced in dogs and then intravenous injections of 50 per cent dextrose, 15 per cent and 0.45 per cent sodium chloride, Ringer's solution and distilled water were given. Isotonic solutions increased the drainage and diluted the cerebrospinal fluid. Hypertonic solutions at first increased the drainage, but this was reversed and the spinal fluid became concentrated. In one of these experiments air was drawn up into the ventricles. Hypotonic solutions produced the same effect as Ringer's solution but distilled water produced very little change.

N ENZLER

COMPARISON OF THE PATHOLOGICAL EFFECTS OF PROLONGED EXPOSURE TO
CARBON MONOXIDE WITH THOSE PRODUCED BY VERY LOW OXYGEN
PRESSURE J ARGYLL CAMPBELL, Brit J Exper Path **10** 304, 1929

It is shown that in chronic carbon monoxide poisoning in animals the pathologic effects resemble very closely those of prolonged exposure to very low oxygen pressure in the inspired air, the main changes are venous congestion with atrophy of certain cells (e.g. liver, heart muscle near the epicardium), edema and dropsy indicating that heart failure is the cause of inability to tolerate prolonged exposure to carbon monoxide. The organs showing most marked congestion and its sequelae are the liver, lungs, heart muscle near the epicardium and the brain. Haldane's view that carbon monoxide acts purely by interfering with the oxygen supply to the tissues is supported.

Power to tolerate carbon monoxide—just as in the case of low oxygen pressure in the air—depends on the ability of the vital organs, particularly the heart, to continue to function under a low tissue oxygen tension, tissue oxygen tension is not brought back to normal level by so-called acclimatization under severe degrees of oxygen want.

AUTHOR'S SUMMARY

PULMONARY TUBERCULOSIS AND ACID INTOXICATION, PARTICULARLY LACTIC
ACID F POMPLUN, Beitr z Klin d Tuberk **72** 324, 1929

In patients with slight lesions, the lactic acid values in the venous blood are nearly the same at rest and during exercise. But in far advanced cases, the difference between rest and exercise becomes large, in such cases the values are elevated above the normal, even at rest the elevation being parallel with the amount of pulmonary involvement. In the anaerobic phase of muscular labor glycogen is decomposed to lactacidogen and then to lactic acid. For the oxidation of the latter or for its resynthesis to glycogen, oxygen is needed. Previous studies on gases of the blood have demonstrated the fact that with increased pulmonary involvement, a relative or absolute deficiency of oxygen exists in the arterial blood. This oxygen deficit is the cause for the accumulation of lactic acid, since oxygen is necessary for its normal disposal. This mechanism of decompensation is evident at first only during exercise, and accounts for undue muscular fatigue, with progressing lesions, decompensation exists even during rest in bed, in such cases, the patients are dyspneic at rest.

MAX PINNER

PATHOLOGIC EFFECTS OF IRRADIATED ERGOSTEROL HELENE HERZENBERG,
Beitr z path Anat u z allg Path **82** 27, 1929

The discovery of the antirachitic action of irradiated ergosterol was followed by observations that indicated that this substance has a toxic effect when administered to mature rats in relatively large doses. Among the tissue changes noted was calcification of the aorta. It was primarily to study the vascular changes and to compare them with those of arteriosclerosis and those caused experi-

mentally by cholesterol feeding that the experiments reported by Herzenberg were undertaken. Young and mature rats were used. The ergosterol was introduced directly into the stomach by means of a catheter in variable doses of from 5 to 100 mg. Some of the animals were kept on the usual mixed diet, some on a diet low in calcium and some on the mixed diet to which an excess of calcium carbonate was added. Kreitmaier and Moll had noted pathologic effects in 100 per cent of the animals to which they had administered irradiated ergosterol. Of fifty-five animals used by Herzenberg in her series of experiments, all but two showed alterations of varying degrees of severity. The manifestations of a general effect consisted in loss of appetite and weight, roughening of the coat of hair, diarrhea and hemorrhagic crusts about the nose and eyelids. Young and adult rats on a high calcium diet withstood the effects better and lived longer than adult rats on a mixed diet, some of the former lived from fifty to sixty-four days. In adult animals on a mixed diet, large daily doses of ergosterol had an acutely toxic effect, death occurring as early as the sixteenth day. In such animals necrosis with leukocytic infiltration was noted in the striped muscle of the heart and diaphragm and in the smooth muscle of the aorta, rarely in the smooth muscle of the gastro-intestinal tract and never in that of the urinary bladder or uterus. In experiments of longer duration, calcium was deposited in the media of the aorta and its branches down to the smallest arteries except those of the skin, in the veins, in the heart muscle and in the renal, bronchial and gastric epithelium, in the latter situations evidently as the result of calcium excretion. Calcium deposition occurred in the media of the vascular system, even in the absence of necrosis of muscle fibers. The elastic fibrils of the media also became impregnated with calcium. Proliferative changes were not noted in the intima. The arterial process was a pure medial calcification, which the author does not consider arteriosclerotic in character. The widespread calcification might be the result of increased calcium assimilation under the influence of ergosterol or of increased mobilization of calcium from the bones. The latter is the explanation accepted by the author, the mobilization being probably the result of an acidosis caused by the ergosterol. Similar arterial changes could not be brought about by the use of epinephrine or chloramine.

O T SCHULTZ

IRRADIATED ERGOSTEROL EXPERIMENTS M SCHMIDTMANN, *Verhandl d deutsch path Gesellsch* **24** 75, 1929

Experimental results seem to indicate a discrepancy between the results of irradiated ergosterol feeding in human beings and experimental animals. There were marked fatty changes in the arteries of rabbits and cats after from eight to fourteen days of feeding two drops of irradiated ergosterol per day. In young animals, death occurred in two ways after large doses. Some animals died a sudden toxic death after several days and postmortem examination showed parenchymatous degeneration and petechia in their organs. Others had chalk cylinders in their kidneys and calcification in the parenchyma. At times this was accompanied by bladder stones and pyonephrosis.

GEORGE RUKSTINAT

POSTOPERATIVE KETONURIA M MOGILEW, *Zentralbl f Gynak* **52** 1216, 1928

In 100 surgical gynecological cases a preoperative ketonuria was observed in 11 per cent of the cases and a postoperative one in 67 per cent. Starvation, increased by the use of laxatives, and the psychic status of the patient are regarded as the cause of the preoperative ketonuria, while starvation, operative trauma, anesthesia, psychic status and other factors influencing the vegetative nervous system are considered as cause of the postoperative ketonuria. The ketonuria lasts usually to the fourth day after operation. Preoperative prophylactic treatment with insulin and dextrose resulted in disappearance of the postoperative ketonuria.

W C HUEPER

Pathologic Anatomy

ACUTE OBSTRUCTION OF THE CORONARY ARTERY JAMES B HERRICK *Am Heart J* 4 633 1929

This condition is usually caused by a thrombus in a vessel, the wall of which shows chronic retrograde processes. These chronic changes may not be the only factors in causing the thrombus to form. Other factors may be (1) emboli from intracardiac thrombi formed over myocardial infarcts (2) infectious processes in other parts of the body (3) coronary phlebitis and (4) physical and chemical changes in the blood. The outcome of the lesion depends not only on the suddenness and completeness of the occlusion but also on the size and location of the vessel involved, the amount of collateral circulation, the condition of the intact portion of heart muscle and the capacity of the infarcted area to heal by scarring.

PEARL ZEEK

DISTORTION OF THE BRONCHI BY LEFT AURICULAR ENLARGEMENT J M STEELE and R PATERSON *Am Heart J* 4 692 1929

Enlargement of the left auricle may exert pressure on the esophagus and main bronchi but this phenomenon rarely gives rise to changes in the lung. However it may frequently be found by x-rays and thus aids in the diagnosis of left auricular enlargement.

PEARL ZEEK

INTESTINAL PNEUMATOSIS ROBERT A MOORE *Am J Dis Child* 38 818 1929

Four cases of intestinal pneumatosis in infants are reported. The pathologic picture is the presence of gas in endothelial lined cysts of the intestinal wall with a chronic productive inflammation in the surrounding tissue. The gas is derived from the intestinal lumen and enters the wall by a mechanical process through an ulceration in the mucosa.

AUTHORS SUMMARY

THE HEPATIC LESION IN ECLAMPSIA W J DIECKMANN *Am J Obst & Gynec* 17 454 1929

It is assumed that incompletely digested proteins placental or intestinal in origin find their way into the circulation and cause damage to the hepatic endothelial cells and shorten the coagulation time of the blood. These substances are of greatest concentration in the portal circulation and cause thrombosis in the larger and smaller portal branches of the liver and peripheral necrosis of the hepatic lobule. Histologic changes in the liver of dogs that closely resemble those of eclampsia may be caused by injecting tissue fibrinogen directly into the portal vein.

A J KOBAK

DECIDUAL FORMATION ON THE PERITONEAL SURFACE OF THE GRAVID UTERUS I HOFBAUER *Am J Obst & Gynec* 17 603 1929

Ectopic decidual cell formation was noted in fifteen of twenty uteruses. These cells were located in an area roughly triangular on the posterior surface of the uterus in the folds made by the broad ligaments and uterus with the apex extending almost to the insertion of the ovarian ligament. Grossly this area looks rough and has a dull sheen. The decidual-like cell has its origin in the cells which are present in the connective tissue layer beneath the peritoneal mesothelium. The cells are spindle-shaped with a dark ovoid nucleus and scanty cytoplasm. They may also simultaneously undergo metaplasia into unstriated muscle fibers. This cell is therefore considered to be an undifferentiated type of cell retaining its mesenchymal potentialities and responds to varying stimuli to form either decidual cells or muscle fibers. The cells of the peritoneal endothelium in some cases

were observed to undergo metaplasia and become cylindric and closely resemble that of the decidua vera. The author discusses the part played by hormones in producing these changes particularly that derived from the anterior lobe of the hypophysis

A. J. KOBAK

OBLITERATION OF THE VERMIFORM APPENDIX C. A. HELLWIG, *Am J Obst & Gynec* 18 332, 1929

Of 859 appendices obtained at operation, 60, or 7 per cent, showed atresia of the lumen. In 56 per cent only the distal third was occluded, and in the others the whole organ. The microscopic picture of the obliterated appendices did not correspond to the descriptions as given by Ribbert, Sudsuck and Oppenheim, who studied autopsy material. Far from being uniform, it was of the greatest variety. In more than one half of the cases leukocytic infiltration and cellular granulation tissue was found which indicated that an inflammatory process had not completely subsided or that a healing stage of acute appendicitis was complicated by recurrence. Signs of healed appendicitis were found in about two thirds of the specimens and consisted of scar formation in the external layers. The histologic examination of the nonoccluded portion revealed pathologic changes in two thirds of the partially obliterated appendices, and in one half of these the inflammatory changes were recent. All stages from acute purulent inflammation to the healing stage and to terminal fibrosis were present, leading to the conclusion that the atresia is the final stage of ulcerative appendicitis in which the epithelial tissue is completely destroyed.

AUTHOR'S SUMMARY

ABNORMALITY OF THE CEREBRUM AND LEPTOMENINGES SIMULATING AN INTRACRANIAL TUMOR R. C. BUCKLEY and E. M. DELRY, *Am J Path* 5 459, 1929

A localized abnormality of the right cerebral hemisphere was found after death in the brain of an infant suspected during life of having a tumor of the brain. The lesion, when disclosed, was thought to be an unusual tumor, until the brain came to be sectioned. Had this lesion been exposed at operation, it might easily have been mistaken for an enucleable tumor, and had a fragment of one of the localized thickenings of the meninges been taken for immediate diagnosis, the tissue might well enough have been reported as a glioma.

AUTHOR'S CONCLUSION

PATHOLOGIC HISTOLOGY OF ADRENALECTOMIZED CATS H. E. MACMAHON and R. L. ZWEMER, *Am J Path* 5 491, 1929

The gross and microscopic lesions following experimental adrenal insufficiency in cats (average survival ten days) are described. Briefly, they consist in fatty degeneration of the tubules of the kidney, lymphoid hyperplasia, moderate colloid distention of the thyroid and hyperplasia of the interstitial cells of the testis. The significance of these and other observations on experimental adrenal insufficiency is discussed in relation to "lipoid nephrosis," lymphoid hyperplasia and additional clinical syndromes.

AUTHORS' SUMMARY

CONGENITAL ANOMALIES OF THE LIVER H. E. MACMAHON, *Am J Path* 5 499, 1929

Congenital anomalies of the liver are relatively infrequent. They may involve the biliary system, the liver cells or the stroma. Several of the more common types are described and explained on an embryologic basis. One type that is characterized by an increase and dilatation of the periportal bile ducts, accompanied by an increase in connective tissue in the portal areas, may persist throughout life. Associated with this type of anomaly are the congenital cysts of the liver occa-

sionally seen at birth and also in later life. Moreover, this anomaly, with or without cyst formation commonly accompanies bilateral congenital cysts of the kidneys.

AUTHOR'S SUMMARY

CARCINOID TUMORS OF THE APPENDIX C. L. WILMOTH, Ann Surg **90** 261, 1929

In view of the present knowledge of carcinoid tumors, they are to be regarded in a similar relation to carcinoma as giant cell tumors are to osteogenic sarcoma. Emphasis is placed on the benign character of these growths. The origin of the carcinoid cells is explained on the conclusions which have been reached by Masson and Forbus by use of the ammoniacal silver stains. Although the tumors are practically benign, nevertheless they may assume malignant characteristics, but the author makes no statement regarding the cases which have been reported.

RICHARD A. LIFENDAHIL

CONGENITAL MEDIASTINAL CYSTS OF GASTROGENIC AND BRONCHOGENIC ORIGIN C. G. MINTER and S. H. CLIFFORD, Ann Surg **90** 714, 1929

Congenital mediastinal cysts occurred in three infants under 3 months of age. In two, a gastrogenic origin was warranted in that the cysts contained typical gastric mucosa. Their size was sufficient to cause displacement and atelectasis of the lung. The cystic fluid was opalescent, viscid, acid in reaction and had a specific gravity of 1.010, it was rich in polymorphonuclear leukocytes. This fluid differs from the oily material in dermoids, which in addition contain cholesterol crystals or squamous epithelium. The authors attribute these cysts to a pinching-off of outbuddings or diverticuli of the foregut with entoderm and mesoderm being carried downward by the growing lung thus lodging in the mediastinum or on the surface of the lung. The third case reported is a similarly located cyst but of bronchial origin which was covered by pseudostratified ciliated columnar and low cuboidal epithelium overlying cartilaginous tissue. This type arises by a pinching-off of diverticuli of entoderm and mesoderm from the foregut in the region of or from the tracheal bud itself. The dermoid cysts are formed at an earlier period, and the teratoma represents a primitive type of cell inclusion.

RICHARD A. LIFENDAHIL

CHRONIC FIBROUS OSTEOMYELITIS D. B. PHEMISTER, Ann Surg **90** 756 1929

Circumscribed areas of bone destruction that were filled with soft tissue, in eleven cases afforded the opportunity for this study. In the earliest stages the cavity is filled with soft grayish-brown tissue containing fibroblasts, capillaries, polyblasts, old blood pigment and usually areas of more or less necrosis. The surrounding bone tissue may or may not respond by the formation of new bone. From two of the specimens, *Staphylococcus aureus* was cultured. Trauma could not be regarded as an etiologic factor. In the author's opinion, aseptic necrosis as the result of anemic infarcts is not sufficient to cause the lesion but possibly additional bacterial infection may be adequate to produce it. The organism is classed in the pyogenic group and therefore the typical inflammatory response is absent in the cytologic picture.

RICHARD A. LIFENDAHIL

MASSIVE PULMONARY ATELECTASIS (COLLAPSE) HERMAN HENNEIL, Arch Int Med **44** 604 1929

The cases of massive collapse may be due to (1) bronchial obstruction from within (foreign body, endobronchial neoplasm, blood clots, diphtheric membrane, etc.) (2) interference with respiratory movements from muscular paralysis or inhibition, faulty posture, long continued, etc., leading to collapse from occlusion.

of bronchial lumen by accumulated secretions, (3) extrabronchial pressure (neoplasm, aneurysm, enlarged lymph glands) In bronchial occlusion from whatever cause the alveolar air is absorbed and pulmonary collapse occurs

AUTHOR'S SUMMARY

THE PATHOLOGY OF THE PANCREAS IN NONDIABETIC PERSONS SHIELDS
WARREN, Arch Int Med 44 663, 1929

The pancreatic lesions in 156 autopsies on unselected nondiabetic patients are summarized Practically any lesion found in the pancreas of diabetic patients can be duplicated in the pancreas of nondiabetic patients, although the frequency of occurrence of lesions of the islands is much less in the latter group Interstitial pancreatitis occurs too frequently in nondiabetic patients to be considered a characteristic lesion of diabetes In many cases, lipomatosis is related to the amount of body fat It is impossible from a study of the pancreas to diagnose the presence or absence of diabetes

AUTHOR'S SUMMARY

TUBERCULOSIS OF THE AORTA LEYLAND J ADAMS Arch Int Med 44 711,
1929

Thirty-six cases of tuberculosis of the aorta have been reported The case cited here is the twentieth reported instance of tuberculosis reaching the aorta by extension from a tuberculous process outside the aorta In this case the involvement extended to the media, but no rupture occurred Clinically, syphilitic aortitis was suspected on account of the history, shortness of breath, pain, pallor and the positive Wassermann reaction

AUTHOR'S SUMMARY

DIENCEPHALIC AUTONOMIC EPILEPSY (CHOLISTATOMA OF THIRD VENTRICLE)
W PENFIELD, Arch Neurol & Psychiat 22 358, 1929

A woman, aged 41, had been suffering from occipital headaches since an accident to her head at the age of 5 When they were severe she would have attacks of dizziness At the age of 28, during an attack the patient stiffened, fell under the table, was unconscious for several hours and apparently had a convulsion which involved the arms, legs and neck At the age of 36 she began to show recurring seizures The attacks would always begin by the patient asking for ice, then her face and arms would flush a deep red, respirations would become slow, tears would roll down the pillow, profuse general diaphoresis would appear and saliva would run out of the corner of the mouth The eyes were open and protruding, the pupils were large and the pulse was strong and rapid Gradually the flushing would fade, the pulse would become weak and slow Respirations were of the Cheyne-Stokes type, and while the patient was breathing, goose-flesh would show on the forearms The attacks were usually followed by shivering Hiccup was an annoying and frequent symptom especially after drinking During some attacks the patient was unconscious and incontinent, the duration of the attacks was from five to twelve minutes The repeated attacks resembled status epilepticus and could for a time be controlled by sodium bromide Aside from the attacks the patient showed a papilledema, diminished hearing bilaterally, normal visual fields, enormously dilated lateral ventricles, absence of air in the third ventricle and disappearance of headaches after turning the head or changing its position The diagnosis of tumor of the third ventricle was made, and the tumor was to be removed, but four hours before the time set for operation the patient died Necropsy disclosed a tumor in the nature of a cholesteatoma in the anterosuperior portions of the third ventricle It protruded into the foramen of Monro and pressed on the mesial anterior and superior aspect of the thalamus of each side Histologically, the optic thalamus was practically normal except for a small portion where the tumor impinged and caused a recent edema and cavitation with the fading-out of

cell structure The edematous area extended as far as the anterior commissure The convulsions, called autonomic by Penfield, were in his opinion caused by the tumor which periodically pressed on the optic thalamus, causing irritation of some centers or conduction path in the thalamus "capable of setting into action the ganglia which exert control over vascular apparatus, sweat and tear glands, etc"

G B HASSIN

PROLIFERATION OF THE ARACHNOID CELL IN AND AROUND THE DURA MATER
THOMAS WILLIAM BROCKBANK, Arch Neurol & Psychiat **22** 444, 1929

The presence in the dura of small nodular or vesicular outgrowths and their possible relationship to endothelioma have been studied by Brockbank in fifty-nine cases The cases comprised patients of various ages, below 20 to 80, and also a variety of pathologic conditions such as tumors, meningitis, hydrocephalus, cerebral hemorrhage and eleven apparently normal persons One gains the impression that the growths are proliferated arachnoid cells which form clusters "against" the dura and within the dura, and even force themselves through the latter The growth has something to do with the increased intracranial pressure, but has little if anything to do with the age, as a matter of fact, it may occur in normal intracranial conditions, and the groups of the proliferating arachnoid cells may have characteristic whorls such as are found in endotheliomas

G B HASSIN

BLASTOMYCOTIC MENINGO-ENCEPHALITIS ISTVÁN GÁSPÁR Arch Neurol & Psychiat **22** 475, 1929

Blastomycosis usually appears as a cutaneous form and very seldom as a generalized form In Gaspar's patient the cerebral meninges and the brain itself were involved—an extremely rare occurrence The clinical symptoms were pain in the head and neck, tenderness over the occipital region, horizontal and vertical nystagmus, slight choking of the disks, some rigidity of the upper extremities and difficulty in walking As a rule, the temperature was normal The spinal fluid showed a marked increase in globulin, 35 cells per cubic millimeter and a pressure of 30 mm of mercury A ventriculogram was attempted but was unsuccessful A subtemporal decompression gave a temporary improvement but two months later the patient developed difficulty in speech and convulsions At a second operation an encapsulated growth was found over the rolandic area It was firmly adherent to the dura and was 6.5 cm in diameter and 2 cm thick Its internal layer infiltrated the brain tissue and was made up of milary abscesses enveloped by connective tissue Some fibroblasts grew among the leukocytes and were united with giant cells The intermediate layer of the tumor contained numerous necrotic areas surrounded by hyaline connective tissue This was abundant in the external layer of the tumor in which abscesses were absent The microscopic diagnosis was chronic blastomycotic meningitis with formation of a large granulomatous mass The blastomyces were well stained with the method of Levaditi However, their presence is not necessary for differentiation from a tubercle, which the granulomatous mass resembles, it differs from a tubercle in the presence of abscesses and in the absence of the rampart of round cells around the focus which is common in a tubercle

G B HASSIN

THE ORIGIN OF OLIGODENDROGLIA IN CEREBRAL TUMORS ARMANDO FERRARO,
Arch Neurol & Psychiat **22** 511 1929

The study of a pontocerebellar angle tumor, which looked like a neurinoma, macroscopically, showed it to be a mixed tumor of glial nature Some areas were typical of spongioblastoma multiforme, ependymal cells predominated in some, and astrocytes in others In addition, microglia cells predominated in some areas Intermediary stages between normal cells and glial cells could be well followed up especially in areas undergoing degeneration In some areas the microglia cells

exhibited the "pseudopodic" appearance which according to Hortega occurs in the immature stages of the microglia development. For such areas containing immature microglia cells, Ferraro would suggest the term microgloma. In other parts of the tumor oligodendroglia cells predominated, forming clusters, they were also scattered elsewhere. Some showed transitional stages in the form of astrocytes, a fact which reveals the common origin of these two types of cells. The oligodendroglia cells which Ferraro succeeded in staining were also scattered among the cells of the spongioblastic type. Careful study of transitional cell forms led Ferraro to the conclusion that "oligodendroglia cells are derived from a transformation of the secondary spongioblasts," that is, from the unipolar cell. He also found areas of spongioblasts coexistent with those of oligodendrogloma which in his opinion is a further argument that the oligodendroglia cells are derived from the spongioblasts.

G B HASSIN

THE STRUCTURAL CHANGES FOLLOWING CENTRAL TRAUMA E. A. LINELL,
Arch Neurol & Psychiat **22** 926, 1929

Linell repeated the experiments of Penfield with aseptic injuries to the brain. He studied the reactions of the glia produced for the purpose of ascertaining the functions of the various types of the supporting elements of the central nervous system. Since the work of Cajal and his school as such are recognized macroglia (fibrillary and cytoplasmic astrocytes), microglia (also known as Hortega cells) and oligodendroglia (generally known as glia nuclei). For these experiments a series of ten rabbits was used. The brain was injured through the insertion of an ordinary blunt probe from 1 to 3 cm. into the brain tissue or by insertion of a glass tube sharpened at the end and drawn out to a sufficiently fine caliber to pass through the burr holes. The rabbits were killed by chloroform at periods varying from three days to two months after the date of the brain wound. Fixation was in Cajal's formaldehyde bromide solution, and the staining methods were Penfield's modification of the Hortega's silver carbonate technique and other methods of the Cajal school. Reactive signs to the injury of the brain may show on the part of both the macroglia and microglia as early as the third day following the injury. The microglia has mainly a phagocytic function of scavenging the damaged tissue, especially the myelin. This activity reaches its maximum within about six days after the injury. The gradual transformation in so-called gutter cells can be followed up. The macroglia, however, showed its maximum reaction at three weeks, but its function is especially noticeable in late stages when it plays the principal role in formation of a brain scar tissue. At the end of two months the margin of the wounds is represented by a glial feltwork which begins at four weeks and a paucity of recognizable astrocyte cell bodies. The glial scar formed is the terminal result of the macroglia reaction.

G B HASSIN

CHANGES IN THE SPINAL CORD IN ANEMIA ARTHUR WEIL and CHARLES
DAVISON, Arch Neurol & Psychiat **22** 966, 1929

Weil and Davison studied histologically the spinal cords in ten cases of pernicious anemia, seven cases of carcinomas of the stomach with secondary anemias, fourteen cases of various types of malignant conditions with secondary anemias, six cases of Hodgkin's disease with secondary anemia, three cases of lymphosarcoma with secondary anemia, six cases of tuberculosis with secondary anemia and four cases of leukemias. The purpose of the studies was to establish whether the changes in so-called subacute combined degeneration of the cord occur only in pernicious anemia or also in anemias associated with the foregoing states. For the various types of anemia the classification of Morawitz and Denecke was used, and that of Henneberg for the various types of changes in the spinal cord. In their material of seven cases of carcinoma of the stomach, only one showed neurologic signs of subacute combined degeneration of the cord, in spite of the presence in all of them of achlorhydria, a high color index and a duration of the disease of

from one to four years. Some of the cases of Hodgkin's disease showed clinical signs of subacute combined degeneration of the cord, but histologically one case showed a degeneration of the pyramidal tracts with Weil's hematoxylin stain, while in another case there was a slight involvement of Goll's columns. The cases of lymphatic and myelocytic leukemia showed no clinical or pathologic manifestations. Weil and Davison's conclusion is that the current opinion that all types of anemias may cause subacute combined degeneration of the cord should be modified. The etiology should be limited to hemolytic anemia, especially to the progressive pernicious form and, in rare cases, also to hemolytic anemia from other causes, for example, that caused by infestation with *Bothriocephalus latus*.

G B HASSIN

OCULAR DISTURBANCES IN EPIDEMIC ENCEPHALITIS F KENNEDY, Arch Ophth
1 346, 1929

Forcible spasmodic shutting of the eyes may occur. This belongs in the same category of release phenomena as spasmodic torticollis. Ptosis of the eyelids is a frequent symptom of encephalitis and is often found in association with weakness or paralysis of both external recti. Blepharospasm also occurs and is due to involvement of the third nerve or nucleus.

Transient diplopia, usually unaccompanied by strabismus is perhaps the most frequent single diagnostic feature of the early stages of encephalitis.

There is apt to be a special lymphocytic infiltration in the region of the quadrigeminal plate near or in the oculomotor nuclei. This produces the Parinaud syndrome (a diminution or loss of conjugate associated movements of the eyeballs upward or downward). These disturbances occur with sudden onset commonly in the acute stages of the disease but may be slowly progressive in chronic cases. In the latter there is a widespread neuroglial proliferation and degeneration of vascular walls with numerous thrombi and small hemorrhages.

The subependymal, peri-aqueductal changes are the cause of the not rare appearance of an Argyll Robertson pupil in encephalitis. One may also find paresis of accommodation which is usually bilateral. Nystagmus is almost the rule in acute encephalitis, both the cerebellar and labyrinthine varieties. True retrobulbar neuritis is rare, papilledema is not common. Optic neuritis occurs late in the disease and is due to sudden blocking of interventricular drainage by meningitic exudate.

CHARLES WEISS

PYELITIS, URETERITIS AND CYSTITIS CYSTICA J J JOELSON, Arch Surg
18 1570, 1929

The author reports a case of this interesting lesion of the urinary tract which was bilateral and which was associated with nephrolithiasis. The diagnosis was made by ureterograms and pyelograms.

N ENZER

TRAUMATIC ARTHRITIS HISTOLOGIC CHANGES IN HYALINE CARTILAGE M N
SMITH-PETERSEN, Arch Surg 18 1216, 1929

From a comparison of sections of the sacro-iliac joints in normal persons with those from patients having a history of recurring strain in this joint, one finds that the hyaline cartilage undergoes a cycle of changes beginning with a surface fibrosis which later shows a myxomatous degeneration. This in turn is invaded by fibrous tissue replacing the matrix, and, finally, calcification.

N ENZER

INTRACRANIAL SARCOMATOSIS OF LEPTOMENINGEAL ORIGIN PERCIVAL BAILEY,
Arch Surg 18 1359, 1929

The reviewer may perhaps be excused for a little more than ordinary enthusiasm over this article. It is a scholarly review which embraces the investi-

gations concerning the embryology of the meninges and the origin of a series of rather rare tumors. Bailey points out that a great deal of the evidence points to the leptomeninges as having a neuro-epidermal origin. Nevertheless, the fact that there are tumors having a fibroblastic structure makes their histogenetic classification somewhat difficult, and he warns against a too schematic consideration of these structures. The advisability of the use of the term sarcoma may be in question, but the fact that they do differ from other intracranial tumors of neuro-epidermal origin supports the use of this term, especially from a descriptive standpoint. The first group he described consisted of several peritheliomas. These tumors characteristically spread over the meninges to form a so-called sarcomatosis or endotheliomatosis, and all of them have occurred in adults after the age of 30. On the other hand, a similarly invading tumor of nerve tissue origin almost always occurs in children, and these are composed of a peculiar type of cell from which Bailey and Cushing have called these tumors medulloblastomas. The microscopic appearance of these tumors is characteristic from several standpoints: first, the characteristic perivascular layer of cells, and the fact that these cells form a reticulum. The tumor grows in these perivascular arrangements, and may arise spontaneously from several foci. In its advancement it leaves a shell of sclerotic brain tissue between the islands and intervacular characteristic areas of necrosis occur, which is different from the small cell medulloblastoma. He described a similar tumor which probably took origin from the leptomeninges and encroached on the brain tissue without invading it. Of a group of perithelial sarcomas he describes two in which the cells are more nearly spherical, and which also show a similar characteristic reticulum. Mitotic figures here are numerous, and the tumor is more malignant. Fibroblastomas are included for consideration, and in these there is a dense, spindle cell structure. An alveolar sarcoma is described in which the reticulum is of especial importance, and a distinguishing feature between the medulloblastomas and neuro-epitheliomas as opposed to sarcomas is the fact that the nuclei of the reticulum cells are particularly prominent in the former. In discussing the tumors which have melanotic cells in them, he points out that this might be strong evidence of a neuro-epidermal origin, but at the same time a dopa reaction has not been obtained from them. The article is extremely well illustrated, and an abstract could hardly do it justice. The study of these rare tumors is mainly interesting from the standpoint of theoretical pathology, but nevertheless may be useful in the study of the embryology of the leptomeninges.

N ENZIR

ELASTIC TISSUE IN MENINGIAL FIBROBLASTOMAS, SO-CALLED DURAL ENDOTHELIOMAS. W. P. VAN WAGENEN, Arch Surg **18** 1621 1929

This article is illustrated with sections from a tumor of a fairly dense cellular structure, in which elastic tissue fibrils were demonstrated. These fibrils were found some distance from the dura, and from their abundance the author feels that they were not derived from the stroma. They were closely related to the tumor cells. Also, he observed that fibroglia fibrils were fused together into elastic tissue fibrils. He agrees with Penfield in the terminology of meningeal fibroblastoma as opposed to endothelioma.

N ENZIR

BRANCHIAL APPARATUS. O. R. HAYDMAN and G. LIGHT, Arch Surg **19** 410, 1929

This is an extensive review of the history, anatomy and embryology of the branchial areas, and an analysis of cysts and fistulas, with a differential diagnosis and a description of the pathologic process. A table of sixty-one cases selected from the literature is included. The authors feel that these anomalies are due to ectodermal and entodermal epithelial inclusions. There is a tendency to familial

occurrence transmission being through the maternal side They offer a simple classification of branchial cleft epidermoid cysts and branchial cleft mucous cysts

N ENZER

LYMPHATIC DRAINAGE FROM THE PERITONEAL CAVITY IN THE DOG G M HIGGINS and A S GRAHAM Arch Surg 19 453, 1929

The authors used a method of graphite injection into the peritoneal cavity, and studied the lymphatics in the upper peritoneal areas and on the surface of the diaphragm From their observations they conclude that the removal of graphite in the dog is largely through the diaphragmatic lymphatics and the sternal branches The pigment appears in the sternal lymphatic channels long before it does in the thoracic duct They do not feel that the thoracic duct plays an important part in lymphatic drainage of the peritoneal cavity The infected pigment appears in the lymph nodes at the upper portion of the chest wall relatively early and is both intracellular and living free, whereas in the thoracic duct when it does appear, it is nearly always extracellular From an hour to an hour and a half elapsed before the graphite was found in the thoracic duct, whereas it appeared very early in the sternal lymph channels The cells in the thoracic duct which did contain graphite were similar to the cells found in the peritoneal cavity

N ENZER

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE L R WHARTON and F H KROCK Arch Surg 19 848, 1929

The authors claim that there are about 230 cases of this lesion on record and they now present a review of 14 The relationship of salpingitis is commented on It probably does not bear an important etiologic relationship to the onset of malignancy, and it is difficult sometimes to determine whether the inflammatory reaction found at the time of operation is primary or secondary to the tumor growth The dissemination of the tumor depends largely on whether or not the frimbriated end will be closed If it is not, the tumor is early implanted into the peritoneum The tumor arises in the mucous membrane, and may give rise to a papillary or alveolar growth or combinations of both of these In some instances one finds a papillary hyperplasia of the tube in which the cells do not appear to be malignant, and yet the structure is that of a malignancy Finally, these papillae may show malignant change The growth is usually inward toward the lumen of the tube, and finally the mass fills and distends the tube before invasion of the muscularis occurs Often bilateral metastases occur early and are widespread

N ENZER

LEUKOPLAKIA OF THE RENAL PELVIS A A KUTZMAN, Arch Surg 19 871, 1929

Including the author's case sixty-seven cases of this lesion of the renal pelvis are on record This article includes a tabular summary The etiology is unknown, and is most frequently discovered after the kidney has been removed for some other lesion, especially infections, or stone One of the important phases of the study of this condition is its relationship to malignancies of the renal pelvis, and of the sixty-seven cases 11.9 per cent contained carcinomas, seven of which were squamous cell The appearance of the leukoplakia in the renal pelvis is apparently not different from leukoplakic patches elsewhere The lesions present the characteristic layers of squamous epithelium except that cornification is not completely developed Several variations in degree of differentiation are recognized The most likely theory accounting for this condition is that of metaplasia under the influence of some chronic irritation It is most common in the fourth decade does not give any characteristic clinical signs, and occurs as frequently in the right or the left kidney, and in both sexes

N ENZER

GROSS AND MICROSCOPIC STRUCTURE OF THE THYROID GLAND IN MAN W F RIENHOFF, JR, Arch Surg **19** 986, 1929

This is a most interesting study of the anatomy of the thyroid gland. The method used was the study of large pieces of the gland by wax plate reconstruction and by maceration and microdissection. A lengthy description is given of the technic. The observations that Rienhoff obtained point to there being definite independence of the thyroid acini, that they do not merge into others, that there is no true lobulation of the thyroid gland and that the acini vary in size under normal conditions and still more in hyperplastic states. There is marked variation in the architecture of the gland from field to field, as demonstrated in his illustrations. The article is extremely difficult to abstract, and must be read to appreciate the nature of the work and the extent to which it was carried. The interesting outcome of this work is the fact that there was no demonstration in any of his sections or plates of fetal rests as described by Wolfier.

N ENZER

CHRONIC COPPER POISONING CYRIL J POLSON, Brit J Exper Path **10** 241, 1929

Experiments are reported which are considered to be a fair repetition of the experiments of Mallory, Parker and Nye, in which they believe that they had produced an accumulation of iron-free pigment in the liver and cirrhosis of the organ, following administration of copper acetate. They considered this pigment allied to hemofuscin. Polson finds, however, that copper acetate fails to produce a higher incidence of pigment cirrhosis in the liver than is found in normal controls when all of the rabbits are fed on cabbage, oats, bran and thirds. However, in a series of control rabbits fed on a diet containing mangel-wurzels and turnips there is an accumulation of "hemofuscin" in the livers of 87.5 per cent of the rabbits.

J N PATTERSON

INFLUENCE OF LOCAL METABOLIC PROCESSES ON THE REACTIVE AND REGENERATIVE PHENOMENA OF INFLAMMATION E LEUPOLD, Beitr z path Anat u z allg Path **81** 45, 1928

In the newer conceptions of the nature of inflammation, physiologic and chemical factors receive greater attention than the causative and teleologic phenomena emphasized in the older views of the process. Leupold studied experimentally the effects of chemicals on the reparative and regenerative reactions in inflammation. The chemicals the effects of which were to be studied were dropped several times daily into small incisions made into the skin of white mice. After two or three days, when the wound had closed, the chemicals were injected in 0.5 cc amounts into the skin about the healing wound. The tissues were examined microscopically at varying intervals during from three to ten days after the incision was made. The substances used were such as might be conceived to take part in the local normal metabolism: proteins (albumin, globulin, casein), peptone, amino-acids, urea and ammonium carbamate, fats and their derivatives, as olive and linseed oil, soaps, glycerin, fatty acids, the carbohydrates, glycogen and dextrose, salts (sodium chloride, carbonate and bicarbonate, potassium chloride, magnesium phosphate, sodium and potassium phosphate). These substances were used in varying dilutions of from 1 to 0.0001 per cent. The mineral salts, through their physicochemical properties in the presence of living tissues, more especially through their buffer action and their effect on the H-ion concentration, act as stimuli to cell and tissue proliferation. The organic substances of large molecular structure, namely, the proteins, fats and carbohydrates, through such effects as they may have on H-ion concentration, surface tension and nutrition of the living cells, also cause increased cell proliferation and more rapid regeneration. Such influence in the case of the proteins is dependent on optimum physicochemical conditions brought about by the salts. The oils used caused increased proliferation of epithelium and of lymphatic endothelium, even in the absence of any salt action.

O T SCHULTZ

REGRESSIVE CHANGES IN NORMAL COSTAL CARTILAGE R BOHMIG, Beitr z path Anat u z allg Path **81** 172, 1928

Bohmig reports the results of a gross and microscopic study of costal cartilages obtained from the necropsy service of Schmorl's institute. The age ranged from less than 1 to more than 80 years. The gross examination was based on 484 cases, the microscopic on 301. For microscopic study, the first, third, fifth and seventh costal cartilages were taken. The study was limited to regressive, or perhaps degenerative changes, which may be considered to fall within the range of normal alterations, inflammatory and neoplastic reactions being excluded. Beginning at puberty there occurs a progressive relative increase in ground substance, at the cost of the cellular elements. A decrease in the number of penetrating blood vessels begins in childhood and is due to local nutritional degenerative changes in the perivascular connective tissue. Loss of vascularity is associated with asbestos-like fibrillation of the ground substance and with the formation of cleftlike spaces in the latter. The fibrillation occurs about the blood vessels, the fibrils being arranged at right angles to the latter, and in the subperichondrial growth zone. Medullary spaces, traversed by a meshwork of fibrils, are formed within the substance of the cartilage, the fibrils are the collagenous fibrils of the original ground substance. True ossification was noted more frequently than simple calcification. Except in the first rib, ossification occurs irregularly within the cartilage, and begins in the areas of fibrillation and medullary space formation, usually with the formation first of a fatty marrow. The formation of bone is secondary to the formation of the fatty marrow. The perichondrium takes no part in bone formation. Subperichondrial proliferation of cartilage cells was seen at all ages. Bohmig considers the changes noted by him as primarily degenerative and dependent on nutritional changes brought about by the normal disappearance of blood vessels with age. The primary degenerative changes about the blood vessels are regularly followed by regenerative changes, such as formation of fibrils, fibrillated marrow and bone. The latter changes the author considers cataplastic in nature.

O T SCHULTZ

MALDEVELOPMENT OF UROGENITAL TRACT C VAN GELDEREN, Beitr z path Anat u z allg Path **81** 213, 1928

The author reports briefly two examples of urogenital malformation. The first, in a woman aged 23, consisted of absence of the right kidney and ureter, a symmetrically bicornate duplex uterus, an incompletely septate vagina and persistence of the left inferior vena cava. In the second case, that of a girl aged 17 years, the left kidney and ureter were absent, the uterus was bicornate and duplex and the vagina was subdivided by a complete septum.

O T SCHULTZ

ADENOMA, PSEUDO-ADENOMA, AND MASTOMA OF MAMMARY GLAND P PRYM, Beitr z path Anat u z allg Path **81** 221, 1928

By means of detailed descriptions of selected cases, richly illustrated with pictures in the text, Prym attempts to elucidate the differences between true adenomas of the female breast and areas of nonblastomatous hyperplasia. Such areas occur as nodules of variable size and are fairly well circumscribed in the gross, but are not encapsulated or readily shelled out, as are the adenomas. Such pseudo-adenomas arise as localized areas of hyperplasia in normally differentiated mammary tissue, probably as the result of hormonal stimuli. Evidences of their nonblastomatous character are their closer relation to the surrounding tissue, the relationship of their duct system to that of adjacent tissue and more marked reactive changes in their blood vessels. The most important differential point is the presence within the pseudo-adenoma of adipose tissue, which, according to Prym, never occurs in the true adenoma unless secondarily drawn into the nodule at the periphery. Pseudo-adenomas may show the same regressive

changes as those present in the breast from which they come. The small non-encapsulated nodules, so frequently seen in the mammary gland, and which are usually described as adenomas and presented as evidence that the adenoma may arise from normal completely differentiated mammary tissue, are not true adenomas but pseudo-adenomas. The true adenomas may be arranged in a series which includes at one extreme tumors with actively proliferating ducts, acini and lobules, and at the other extreme completely differentiated tissue with a lobular arrangement, which tissue closely simulates that of the mammary gland. Prym terms such completely differentiated adenomas mastomas, but emphasizes that he applies the term mastoma to circumscribed tumors and not to the diffuse adenomatous proliferation of the entire gland, as was done by Schminke. The intracanalicular fibro-adenoma, for which Prym prefers the descriptive name Spaltenadenom or fissure adenoma, also shows the same gradation of changes from active proliferation to complete differentiation. Prym considers it important from both the clinical and the statistical point of view to distinguish between adenoma and pseudo-adenoma.

O T SCHULTZ

QUANTITATIVE AND QUALITATIVE MORPHOLOGIC REACTIONS OF THE SUPRARENAL GLANDS OF THE GUINEA-PIG TO CERTAIN STIMULANTS. R. KOJIMA, Beitr z path Anat u z allg Path **81** 264, 1928

In order to evaluate the changes caused by amanita toxin in the suprarenal glands of the guinea-pig, Kojima studied these glands in normal and starved animals and in a small number of animals subjected to ether narcosis and to the injection of gelatin solution into the abdominal wall. He paid particular attention to the size of the organs in relation to the body weight, to the relative proportions of medulla and cortex, to the relative thickness of the layers of the cortex, and to the microchemical reactions of the cells. The left suprarenal gland is normally larger than the right, and the relation of the total weight of the organs to the total body weight is as 1 to 5,405. In starved animals the weight is absolutely and relatively increased, the relation to the body weight being at 1 to 2,607. In the starved animal the zona glomerulosa is decreased in thickness, the zona reticularis increased. The capillary endothelium of the normal cortex contains yellowish pigment; this is increased in pregnant and in starved animals. Much iron-containing pigment is present in the parenchymal cells of the cortex, especially those of the zona reticularis; this is greatly increased in starving animals. Neutral fat is present normally in the zona glomerulosa and the zona reticularis. Anisotropic lipid material is not normally present in the cells of the zona glomerulosa and zona reticularis, but is present in large amount in the middle portion of the zona fascicularis. Anisotropic lipoids are decreased in the suprarenal glands of starved animals; isotropic lipoids may be either increased or decreased. In normal pregnant animals the quantitative relationships of the lipoids are identical with those of normal animals. Nuclear fragmentation and nuclear division occur normally in the zona glomerulosa and in the outer portion of the zona fascicularis. In starvation, degenerative changes are noted in the cortical cells, and the cortex is hyperemic. The cells of the medulla of starved animals contain hyaline droplets; the chromaffin content is not altered in starvation. In the small series of animals subjected to damage by ether or injection of gelatin, the cortex was increased in thickness after from three to six days, the increase being chiefly of the zona reticularis. Brownish pigment was greatly increased in amount in the endothelial cells and in the cells of the zona reticularis.

O T SCHULTZ

HISTOLOGY OF VENEREAL GRANULOMA. W. FISCHER and K. VON GUSMAR, Beitr z path Anat u z allg Path **81** 309, 1928-1929

The authors give a condensed summary of the pathologic histology of venereal granuloma, based on a study of material from fifty-two cases. Most characteristic is the parallel course of the numerous newly formed blood vessels perpendicular to the floor of the ulcer. The latter is covered by a layer of fibrin

which contains leukocytes. Each vessel is surrounded by a thick mantle of young cells. The predominating cell type is the plasma cell. Lymphocytes, polymorphonuclear leukocytes, eosinophil leukocytes and mast cells also occur, but are much less numerous than the plasma cells. In the granulation tissue are large mononuclear histiocytes which contain the specific organism, these cells show various degenerative changes. The authors consider the histologic observations characteristic enough to permit making the specific diagnosis, but believe that the diagnosis must rest on the whole microscopic picture rather than on any single element. They emphasize the proliferative reaction of the epithelium at the margin of the ulcer, this is often so marked and atypical as to suggest epithelioma. The specific relation of the organism and its biologic characters are briefly discussed.

O T SCHULTZ

EXPERIMENTAL STUDY OF THE INTERSTITIAL CELLS OF THE TESTIS. E. J. KRAUS, *Beitr z path Anat u z allg Path* **81** 323, 1928

Kraus presents the results of work done five years previous to its present publication. In the interval, much similar experimentation has been published. The work consists of a histologic study of the testis of the cat, with especial attention to the interstitial cells, after a variety of experimental procedures. The latter included roentgen irradiation, transposition of the testis into the peritoneal cavity, transplantation into the lower abdominal wall, successive partial resections of the testis and ligation of the vas or epididymis, these various procedures being followed in some animals by roentgen irradiation. The work was done on young, sexually immature animals, and on older, sexually mature ones. In young animals, the various procedures caused a decrease of both tubular elements and interstitial cells. When such animals reached sexual maturity, provided the germinal cells of the tubules were not completely destroyed, the interstitial cells increased in number at this time. In older animals, the procedures caused relative and absolute increase in the number of interstitial cells, which became most marked after the degenerative changes in the tubular epithelium had passed their maximum, and at a time when proliferation of the most undifferentiated tubular cells was most active. Kraus compares the appearances at this stage with those which precede a period of sexual activity in the species of animals characterized by intermittent periods of sexual activity separated by long inactive intervals. Ligation of the vas or epididymis did not cause an increase in the number of interstitial cells. Reduction of the amount of testicular tissue, by removal of one testis or successive resections, following the various procedures, increased the degree of interstitial cell hypertrophy and hyperplasia. In all the experiments, an essential for proliferation of the interstitial cells was the persistence of viable, undifferentiated germinal cells within the tubules. From his own work and that previously published, Kraus concludes that the interstitial tissue is not an endocrine organ in the sense of Steinach and various other writers, it is not the "organ of manhood," on whose normal functioning the development of the normal secondary sexual characteristics depends. A resorptive function is also denied. The primary function of the interstitial tissue is trophic, the furnishing of necessary specific substances to the germinal epithelium. The transfer of such substances is not a direct one, as has been postulated by some, but occurs by way of the local circulation. In addition to its trophic function, the interstitial tissue also has internal secretory activity, but only in relation to spermatogenesis. In its endocrine activity the tissue is probably correlated in function with the hypophysis or midbrain. The other endocrine organs showed no characteristic changes in the animals studied by Kraus.

O T SCHULTZ

EFFECT OF ROENTGEN IRRADIATION ON RETICULO-ENDOTHELIAL PHAGOCYTOSIS. MARIA SCHWIENHORST, *Beitr z path Anat u z allg Path* **81** 375, 1928

The effect of roentgen irradiation on the phagocytic activity of the reticulo-endothelial system of the spleen, liver and lung was studied in white rats. The

animals were subjected to varying doses of filtered or unfiltered roentgen rays, the details of the roentgen technic are not given. Irradiation was followed by the injection into the femoral vein of a suspension of staphylococci heated to 60 C for one hour. The injection followed the irradiation immediately or at intervals of three and six hours, and one, two and three days. The animals were killed for examination immediately after the injection, or at intervals of five, fifteen and forty minutes, two and three hours, and one, two and three days. In one series of experiments injection of the bacteria preceded the irradiation. In control animals, the sinus endothelium of the spleen, the Kupfer and endothelial cells of the liver, and the septal cells of the lung, as well as the polymorphonuclear leukocytes throughout the body exhibited active phagocytosis of the injected cocci, which disappeared rapidly from the blood stream. In injections made up to three hours after radiation, no definite effect on phagocytosis could be detected, although morphologic cellular changes were already evident. The earliest change noted occurred in the spleen and consisted of pyknosis and fragmentation of the lymphocytes. At three hours the lymphoid follicles of the spleen were decreased in size and the reticulo-endothelial cells of the organs examined were swollen. At six hours the capillaries throughout the body were filled with leukocytes in a state of active phagocytosis. When the injection was made at intervals longer than six hours after irradiation the degree of cellular damage was greater, phagocytosis was much less marked, and cocci remained in the blood stream for much longer periods than in controls. Animals allowed to live after roentgenization and injection of organisms did not live as long as controls subjected to bacterial injection alone. In the former, clumps of nonphagocytosed cocci could be seen in the capillaries. The author concludes from her experiments that irradiation damages the cells of the reticulo-endothelial system and decreases or destroys their phagocytic activity. There was no evidence of increased formation of agglutinins or bacteriolysins, as has been claimed by some writers. An apparent slight stimulating effect of the roentgen rays occurs at the six hour period, when leukocytosis is at its height. The temporary, slightly increased antibacterial activity of the body tissues and fluids at this stage is due to the leukocytosis and to the liberation of pre-formed antibacterial substances from cells injured by the rays. The beneficial clinical effect which may follow irradiation of a localized area of inflammation is due to the same factors.

O T SCHULTZ

EXPERIMENTAL ACUTE PEPTIC ULCER. F. BUCHNER, P. SIEBERT and P. J. MOLLOY, *Beitr z path Anat u z allg Path* 81 391, 1928

The generally accepted view that the acute peptic ulcer is the result of digestion of areas of gastric tissue which have been killed by infarction, the latter being due to disease or spasm of the blood vessels or to spasm of the gastric or duodenal muscle wall, has been opposed by Aschoff. He has maintained that the histology of the acute gastric or duodenal ulcer, as seen in the human being, is not that of tissue which has been infarcted and has died and then undergone digestion. He claimed that it is living tissue which is acted on by the gastric juice and that the reaction is an acute inflammatory one. The harmful action of the gastric juice is not necessarily due to abnormal composition of the fluid, but to disturbance of what Aschoff has termed the normal correlation between gastric juice and gastric wall. This correlation may be disturbed not only by changes in the gastric juice, but also by changes in the gastric wall other than infarction or spasm. The present work, from Aschoff's institute, deals with the experimental production of acute ulcers in the stomach of the rat by means of histamine, the latter being an agent which disturbs the normal gastric juice-gastric wall correlation by leading to the formation of an increased amount of gastric juice of increased acidity. The hypersecretory action of histamine is held to be due to an action directly on the secretory cells. In a series of acute experiments, rats that had been starved for twenty-four hours received one or two subcutaneous injections of histamine in a dosage of 0.06 Gm per hundred grams of body weight. Acute

ulcers were found in 33 per cent of the animals as compared with 6 per cent in animals that did not receive histamine. In another series a hunger day during which the animals received one or two injections of histamine was alternated with a day during which the animal was allowed to eat the duration of the experiment being seventeen days. In this series acute ulcers were found in 80 per cent of the animals receiving two daily injections of histamine in 60 per cent of those receiving a single daily injection and in 40 per cent of those merely subjected to starvation every alternate day. The ulcers were most often multiple and occurred only in the proventriculus, that portion of the stomach devoid of secreting cells and lined by squamous epithelium. This portion of the rat's stomach termed the work portion in contradistinction to the secreting portion is likened to the antral portion of the human stomach with its alkaline secretion. The histologic changes were those of necrosis brought about by the caustic action of the gastric juice and acute inflammation. The authors insist that the lesions could not have arisen as the result of infarction. Action of histamine on the blood vessels the gastric musculature or the vegetative nervous system is excluded by the authors.

O T SCHULTZ

VASCULAR OBSERVATIONS IN LUPUS VULGARIS S BETTMANN, Beitr z Klin u Tuberk 72 208 1929

Capillaries in the margins of lupus play a conspicuous role in the healing process. This fact is well illustrated by capillary photography on the living. This type of observation aids in establishing the diagnosis and in assaying the value of therapeutic measures.

MAX PINNER

FATAL HEMORRHAGE FROM A TRACTION DIVERTICULUM OF THE ESOPHAGUS AND PERFORATED BRONCHUS J HEINE, Deutsche med Wchnschr 55 1135 1929

A Chinaman aged 35, died after repeated massive hemorrhages apparently from the lungs. At postmortem examination a cavity in a mass of tuberculous tracheobronchial lymph nodes was found opening into a traction diverticulum of the esophagus and into the left main bronchus just below the bifurcation of the trachea. A bronchial artery was eroded with massive hemorrhage into the lungs and bowel. (See the report by E O Latimer and J D Willems Chicken-Bone Perforation of the Esophagus with Bacterial Erosion of the Left Bronchial Artery ARCH PATH 6 426 [Sept] 1928)

PAUL J BRESLICH

LIPOID NEPHROSIS O DIEBOLD, Deutsche med Wchnschr 55 1550, 1929

The urine of a girl, aged 24 who died of cardiac decompensation was found to contain globules of fat, large amounts of albumin and hyaline and granular casts. In the blood there were 390 mg of cholesterol and 47.6 mg of nonprotein nitrogen per hundred cubic centimeters. The serum albumin was decreased while the globulin was increased. The blood pressure was 150 systolic and 95 diastolic. At postmortem examination the kidneys each weighed about 300 Gm, and the capsules stripped easily from a smooth yellow surface. On surfaces made by cutting the kidneys the cortex was widened and the tissue was yellowish gray with a cloudy swelling. There were no marked changes of the medulla. Histologically, there were large amounts of lipid substance in fine droplets in the cells lining the tubules in the cortex of the kidney and deposits of fat in the glomeruli which were otherwise unchanged. A marked increase of fat was also noted in the cells of the liver suprarenal glands hypophysis and myocardium and in the ovary. The author believes that the changes in the kidney in lipid nephrosis are only part of a generalized disturbance of fat metabolism which involves all tissues.

PAUL J BRESLICH

EXPERIMENTAL STUDIES OF THE REACTION OF THE LYMPHATIC APPARATUS OF THE SPLEEN DURING HUNGER, HEMORRHAGE AND INFECTION H GROLL, Verhandl d deutsch path Gesellsch **24** 10, 1929

The experiments permitted of the following deductions Extirpation of the lower pole of the spleen produced no histologic alteration in the remainder of the organ Hypertrophy of the splenic follicles occurred one day after infection of the body After hemorrhage, there was a marked proliferation and development of the lymph nodes The spleen possesses definite lymph centers which are not reaction centers, but epithelioid centers which are apparently degenerated lymph centers

GEORGE RUKSTINAT

AN UNUSUAL GRANULOMA OF THE NOSE, THROAT AND MOUTH E J KRAUS, Verhandl d deutsch path Gesellsch **24** 43, 1929

The disease was noted in a blacksmith, aged 60, a horseshoer, aged 30, and a tobacco packer, aged 33 Grossly, the lesion was thickened, had a sloping edge and a granulated, speckled, grayish-yellow floor and resulted in death of the host in from five and one-half to twenty-three months Histologically, the lesion was composed of granulation tissue, small epithelioid cells, giant cells and round and plasma cells Bacteriologically, no specific organism was demonstrable Death was due to hemorrhage from the necrotic granuloma

GEORGE RUKSTINAT

SPONTANEOUS FAT GRANULOMA A J ABRIKOSSOFF, Verhandl d deutsch path Gesellsch **24** 57, 1929

Localized necroses in the subcutaneous fat are recorded in death from practically all causes The author recognizes four types that occurring after the subcutaneous injection of oily medicaments, a traumatic type, a type occurring at the periphery of inflammatory processes, and a spontaneous fat granuloma due to ischemia Various things may occur in these granulomas They may become conglomerate forming tubercle-like structures and then undergo fibrous transformation At times they change into serous cysts or masses of scar tissue Some become partially calcified and have fibrous borders while others become totally calcified

GEORGE RUKSTINAT

THE REACTION IN THE NEIGHBORHOOD OF MALIGNANT GROWTHS W FISCHER, Verhandl d deutsch path Gesellsch **24** 263, 1929

Fischer concludes that there is nothing specific in the inflammatory reaction surrounding malignant growths

GEORGE RUKSTINAT

THROMBOPENIC PURPURA OLGA BYKOWA, Virchows Arch f path Anat **268** 606, 1928

From the anatomic study of two cases, the author concludes that essential thrombopenia is not purely a lesion of megakaryocytes but one affecting the entire blood-forming and blood vascular systems Essential thrombopenia and aleukia hemorrhagica are related conditions A megakaryotoxicosis exists in both conditions but with the remaining primitive cells of the bone-marrow also affected

V C JACOBSEN

THE HEALING OF INCISED WOUNDS OF THE SKIN IN FISH RUDOLF HARABATH, Virchows Arch f path Anat **268** 794, 1928

This is an experimental study of the healing of incised wounds of fish, *Cobitis fossilis*, *Tinca fario* and *Anguilla vulgaris* being used in the investigation The time intervals were from thirty minutes to six months It was found that epithelial

repair of skin wounds occurs more quickly than in warm-blooded animals but with a delay, however, in the formation of the "cell knobs" The basal layer of the wound consists of fibrin The defect in the cutis becomes filled with new cicatricial tissue, the subcutaneous and interstitial connective tissues participating Mitosis in epithelial or connective tissue cells was not observed Fish are insensitive to incised wounds A simple incised wound or an incised wound with loss of substance shows a tendency to infection either with fungus spores or with bacteria

V C JACOBSEN

CROSSED EMBOLISM IN PERSISTENT FORAMEN OVALE A WINKELBAUER and K URBAN, Wien klin Wchnschr 42 1072, 1929

If pulmonary embolism occurs in the presence of an open foramen ovale, an overflow into the arterial system usually takes place at the same time In such cases the left brachial artery and the anovina are involved with special frequency Even small thrombi that ordinarily would cause comparatively slight symptoms on the part of the lungs may call forth in that way severe manifestations, particularly on the part of the brain

AUTHORS' SUMMARY

Pathologic Chemistry and Physics

LIPID STUDIES IN XANTHOMA U J WILE, H C ECKSTEIN and A C CURTIS, Arch Dermat & Syph 20 489, 1929

Chemical analysis of additional xanthomatous tumors confirmed the previously reported results that only from 15 to 2 per cent of the total lipid content of these tumors is cholesterol The case of a diabetic patient in whom xanthomatous lesions appeared and disappeared by manipulations of the diet is described In addition, xanthomatous lesions occurring with symmetrical distribution in sisters are reported

FRANK M COCHEMS

RENAL INSUFFICIENCY WITH BENCE-JONES PROTEINURIA EDWIN G BANNICK and CARL H GREENE Arch Int Med 44 486, 1929

The urine should be examined for Bence-Jones protein in all patients with renal insufficiency and when marked proteinuria exists, especially when associated with anemia If this is done many cases of Bence-Jones proteinuria now overlooked may be recognized

THE EFFECT OF CATHODE RAYS ON THE PROTEINS OF SERUM LILLIAN E BAKER and ROBERT B COREY, J Exper Med 50 439 1929

The effects of cathode rays on the proteins of serum appear to be denaturation of a large proportion of the albumin and globulin with the formation of products that are soluble at the p_H of the serum, the production of a tough and exceedingly insoluble substance on the window of the cell where most of the absorption of electrons occurs, a slight hydrolytic cleavage of the protein molecule producing a small quantity of products having properties so near to those of the protein that they are precipitated by trichloroacetic acid but are not removed by coagulation at the iso-electric point, the production of a small amount of hydrolytic products not precipitated by trichloroacetic acid, and the formation of a small amount of ammonia, part of which at least is derived from the urea in the serum It is interesting to note that these changes are such as would bring about exactly those effects on fibroblasts which were observed when cultures were grown in serum which had been subjected to cathode ray irradiation The proteins of serum have a retarding effect on the growth of fibroblasts One might therefore expect their removal by denaturation and coagulation to result in the slightly larger growth which was observed The production of SH groups in the denatured protein

molecule would also tend to have a beneficial effect, as has been observed in experiments with denatured albumin. A concentration of protein split products equal to that in the irradiated serums has been observed to produce cells of characteristic appearance, full of cytoplasmic granulations and possessing long, active pseudopods, such as those noted in colonies cultivated in serum which had been subjected to cathode rays

AUTHORS' SUMMARY

THE RÔLE OF ENZYME ACTION IN THE FORMATION OF DENTAL CALCULI
KENNETH T. ADAMSON, Australian J. Exper. Biol. & Med. Sci. 6 215, 1929

An active enzyme which is capable of hydrolyzing glycerophosphoric ester is contained in the human gum tissue and in the oral tissue of the dog. In the saliva and blood serum there are phosphate-containing complexes (probably in the nature of phosphoric esters) which are capable of being hydrolyzed by the enzyme. The interaction of the enzyme on these phosphate-containing complexes results in the liberation and deposition of free inorganic phosphate. Under favorable conditions the liberated inorganic phosphate will form concretions. The action of the enzyme (liberated by trauma) on the saliva may thus give rise to salivary calculus. The increase in free phosphate in saliva, accompanied by an increase in the copper-reducing power on hydrolysis with 0.1 N acid points to the fact that the organic phosphate is in the nature of a phosphoric ester, probably of the hexosephosphoric group. Human oral gum tissue does not contain pyrophosphatase in any estimable quantity.

AUTHORS' SUMMARY

SOLUBLE SULPHUR COMPOUNDS IN THE ERYTHROCYTES E. GABBE, Klin. Wchnschr. 8 2077, 1929

A method was described for determining the sulphhydryl compounds of the blood, glutathione and thionine, which is based on the oxidation of the SH group with potassium ferrocyanide in acid medium. By this method, from 24 to 46 mg per hundred cubic centimeters of normal blood was found, calculated as glutathione, which was contained in the erythrocytes. In the arterial blood, only from 42 to 75 per cent of the quantity of SH groups demonstrated in the venous blood was found. This indicates a corresponding conversion of the SH forms into disulphide forms in the lungs. An increase of the glutathione content of the blood corpuscles within a few hours was observed in acute anemia, in poisoning with phenylhydrazine and with diminution of the oxygen tension in the inspired air. While the quotient of glutathione and erythrocyte content in normal human blood ranges between 5.3 and 9.3 it increases in secondary anemia to 9.8 and in pernicious anemia to 15.5.

AUTHORS' SUMMARY

THE CHIEF DIFFERENCES IN THE CHEMICAL COMPOSITION OF SKIN VESICAL CONTENT AND INTRAVITALLY REMOVED SKIN TISSUES ERICH URBACH, Klin. Wchnschr. 8 2094, 1929

On the basis of comparative analyses of the blood serum, skin vesical fluid and intravitaly removed skin, the author disagrees with Gaenslen, Wohlgemut and others who contend that the chemical analysis of fluid in cantharides blisters may replace those of the tissues themselves.

AUTHOR'S SUMMARY (in part)

CHEMICAL EXAMINATIONS OF TISSUES WITH EXPERIMENTAL ROENTGEN REACTIONS ERICH URBACH AND HANS SCHNITZLER, Klin. Wchnschr. 8 2179, 1929

Experiments on animals demonstrate that severe protein injury accompanies reactions following roentgen treatments, manifested by an increase in the total nitrogen and nonprotein nitrogen which is dependent in individual cases on the dosage and the interval following the exposure. The increase of the total nitrogen

in the blood is about 10 per cent, and in the skin about from 20 to 30 per cent, while the nonprotein nitrogen of the blood and of the skin is increased as much as 300 per cent. Of these, the uric acid nitrogen is markedly increased. That the reaction is a general tissue damage is indicated by the similarity in kind and degree of alterations in the directly irradiated abdominal skin as well as in the protected skin of the back. There is an inverse ratio between the nitrogen and the chloride values in the skin and in the blood. Variations in calcium, potassium, sugar, cholesterol, etc., are explained by the severe general damage to the organism.

EDWIN F. HIRSCH

Microbiology and Parasitology

VEGETATIVE ENDOCARDITIS DUE TO *BRUCELLA MELITENSIS* CLARENCE E. DE LA CHAPPELLE, *Am Heart J* 4 732, 1929

A case of undulant (Malta) fever due to *Brucella melitensis* is reported which was associated with a vegetative and ulcerative endocarditis of the aortic valves, and which clinically presented the manifestations of subacute bacterial endocarditis. The diagnosis was verified by bacteriologic cultures.

PEARL ZEEK

CONGENITAL SYPHILIS OF THE THYROID GLAND WILLIAM C. MENNINGER, *Am J Syph* 13 164, 1929

Three cases of congenital syphilis showing lesions in the thyroid gland and one clinical report of hypothyroidism in a congenital syphilitic girl are reported. Both hypothyroidism and hyperthyroidism occur with congenital syphilis and in some cases unquestionably are a part of the syphilitic process. Hypothyroidism is more frequent and probably results in most cases from the effect of an intra-uterine toxin, becoming manifest at an early age. Hyperthyroidism is more probably the result of a localization of infectious process in the gland, and usually does not become evident before adolescence. The thyroid may be increased several times in size, may be of normal size and even smaller. It is usually more firm, and several authentic cases of gumma formation have been reported. Microscopically, the gland usually shows a perivascular connective tissue growth of varying degrees, compressing the follicles. The latter are often disturbed in their arrangement with the formation of abnormal colloid and with some increase in vascularity. Spirochetes are sometimes absent and sometimes present in great numbers.

AUTHOR'S SUMMARY

COEXISTENT SYPHILIS AND TUBERCULOSIS A. L. GALLANT, *Am Rev Tuberc* 19 573, 1929

The coexistence of syphilis and tuberculosis, based on the Wassermann reaction, occurred in 21 per cent of the patients treated, in the Kahn test the incidence was 15 per cent. Syphilis coincident with tuberculosis shows a decidedly unfavorable influence on the tuberculosis in direct proportion to the extent and activity. Markedly beneficial effects were obtained by treatment for syphilis, especially when the activity of the tuberculosis was class B or less. The dosage of the arsenicals should be reduced to one-half or one-third the usual amount.

H. J. CORPER

REACTIONS OF THE SUBCUTANEOUS CONNECTIVE TISSUE TO EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG M. L. LINDSEY, *Am Rev Tuberc* 19 615, 1929

As the result of an extensive study in guinea-pigs, it is concluded that the fibroblasts may be considered as an interchangeable source of cells which are involved in maintaining an equilibrium of body cells. They seem to be relatively

undifferentiated cells closely related to primitive mesenchyme. The presence and degree of stimulation of these cells are evidenced by changes in type as the result of this stimulation. Fibroblasts are seen to be transformed into exudate cells, including elasmatoeytes, monocytes, lymphocytes (small histocytes?), polyblasts, epithelioid cells and, as previously shown, plasma cells and mast cells. A new theory of giant cell formation is suggested from the evidence found in this study. There is no evidence for the formation of polymorphonuclear leukocytes from fibroblasts; pyknotic polyblasts may become lobulated and look like pyknotic polymorphonuclear leukocytes the granules of which have disappeared. Monocytes may originate locally from fibroblasts and represent intermediate stages in epithelioid cell formation.

H. J. CORPER

UNDULANT FEVER. A. V. HARDY, J. A. M. A. 93 891, 1929

The characteristics of *Brucella melitensis* organisms have only recently been fully described. A classification of strains isolated from human beings cannot now be regarded as a reliable index of the importance of different varieties as a cause of human disease. A special effort should be made to obtain a detailed postmortem study in all fatal cases of undulant fever. The pathologic lesions and clinical signs of *Brucella melitensis* infections in animals show a definite correlation. The epidemiologic data, based on the reports of more than a thousand recent cases of undulant fever in the United States, indicate that cattle and hogs with contagious abortion are the sources of these infections. Macroscopic agglutination tests on patients with febrile illness of undetermined etiology should be made more frequently. Additional study is essential in order to determine effective and applicable methods of control.

AUTHORS' SUMMARY

ETIOLOGY OF OROFA FEVER. XVI. VERRUCA IN THE DOG AND THE DONKEY. H. NOGUCHI, H. R. MULLER, E. B. TILDEN and J. R. TYLER, J. Exper. Med. 50 455, 1929

In the experiments here reported, definite verruca lesions, in which the presence of *Bartonella bacilliformis* was established by culture or by passage to *Macacus rhesus* monkeys, were produced in a dog and in a donkey by inoculation of cultures or of monkey passage strains. The reaction induced in these animals was entirely local; however, blood cultures were sterile. Histologically, the lesions produced were similar to those obtained in monkeys by inoculation of *Bartonella bacilliformis*, except for the presence of a marked polymorphonuclear leukocytic exudate. In another donkey a lesion histologically suggestive of verruca was produced, while in one donkey and a horse the results of inoculation were negative or indefinite. The intravenous injection of a filtrate or of heat-killed cultures of *Bartonella bacilliformis* into two donkeys was followed by the appearance of large, soft, subcutaneous swellings on various parts of the body, not resembling in any way verruca lesions.

AUTHORS' SUMMARY

DIFFERENTIATION OF HEMOLYTIC STREPTOCOCCI OF HUMAN AND OF DAIRY ORIGIN BY METHYLENE BLUE TOLERANCE AND FINAL ACIDITY. ROY C. AVERY, J. Exper. Med. 50 463, 1929

A grouping of 138 strains of hemolytic streptococci based on differences in dye-sensitiveness and in final hydrogen ion concentration of cultures is presented. Three groups are distinguished, human parasitic strains, defined by a final pH range of 5.2 to 5 and by failure to reduce methylene blue (1:5,000) in milk, bovine strains parasitic in the udder, characterized by a final pH range of 4.5 to 4.2 and by failure to reduce methylene blue (1:5,000) in milk, saprophytic strains, characterized by a final pH range of 4.5 to 4.2 and by ability to reduce methylene blue. Methylene blue was bactericidal for the strains of hemolytic streptococci that fail to reduce it, but neither bacteriostatic nor bactericidal for the strains that caused its reduction.

AUTHOR'S SUMMARY

TONIC SUBSTANCES OF *BACILLUS TYPHOSUS* GREGORY SHWARTZMAN, J Exper Med 50 513, 1929

It has been demonstrated that many multiples of minimal doses of *Bacillus typhosus* reacting factors can be neutralized by specific immune serums. The potency of a given serum can be conveniently titrated against increasing amounts of reacting factors. If the immune serum is diluted or if the amount of the reacting factors is too large for a given amount of serum, neutralization is obtained but only irregularly. Normal and heterologous serums (therapeutic meningococcus and erysipelas horse serums) free from normal agglutinins or possessing normal agglutinins of a low titer (1:16) for *B. typhosus* are not able to neutralize the reacting factors. There is obtained questionable neutralization with a serum possessing normal *B. typhosus* agglutinins in dilution 1:64. The titer of the neutralizing antibodies increases in the course of immunization. Immune serums exercise a definite protection against the mortality induced by the intravenous injection of *B. typhosus* culture filtrates.

AUTHORS' SUMMARY

INFECTIVITY OF BLOOD DURING THE COURSE OF EXPERIMENTAL YELLOW FEVER N. PAUL HUDSON and CORNELIUS B. PHILIP, J Exper Med 50 583, 1929

In five *Macacus rhesus* fatally infected with yellow fever virus, the disease ran varied and typical courses, death occurring from eighty-two hours to ten days after infection. Batches of *Aedes aegypti* were fed daily on each monkey, and specimens of blood injected into other animals. By mosquito transfer, the virus was found to be circulating in the peripheral blood one or two days after the infecting and the same interval before the onset of fever, in one instance, mosquitoes became infectious by feeding on a monkey twelve hours after its inoculation. Mosquitoes continued to acquire infectivity during the febrile period and for one day thereafter, except in one instance in which death occurred during fever which prevented postfebrile testing. By subinoculation of blood, the disease was transferred before and after, as well as during the same interval as in mosquito transmission. In one of two attempts, the virus was carried by this means as early as twelve hours after the donor animal was infected. Following the first day of the postfebrile period, blood transmissions were irregularly fatal beyond the period infective for mosquitoes. These results point to a remarkably rapid multiplication of the virus in the animal host, in one case a blood subinoculation (0.5 cc) being successful at the first test twenty-four hours after the donor monkey was bitten by only two *A. aegypti*. The regular acquisition of infectivity by mosquitoes fed during the incubation period is of especial interest in indicating the infectivity of human cases for mosquitoes before the appearance of clinical symptoms. This offers one explanation for the insidious propagation of epidemics of yellow fever and should be useful in the institution of control activities during an outbreak of this disease.

AUTHORS' SUMMARY

NASOPHARYNGEAL FLORA IN HEALTH AND DURING RESPIRATORY DISEASE IN ISOLATED COMMUNITIES IN ALABAMA AND LABRADOR E. L. BURKA and W. G. SWILLIE, J Exper Med 50 643, 1929

Studies of the bacterial flora of the nasopharynx were made in isolated communities in southern Alabama and Labrador. The basic flora was determined in both communities. In Alabama, an epidemic of common colds was studied. In Labrador, cases of sporadic colds and an epidemic of tracheitis were studied. Gram-negative cocci were found in nearly all normal persons in moderate numbers. In pathologic states, there was a suppression of these organisms. Staphylococci were found in small numbers in about half of the normal persons. In pathologic conditions, they disappeared from most of those affected but were found in increased numbers in a few persons. Pfeiffer bacilli were absent or present only in small numbers in

normal persons During the epidemic of colds in Alabama, there was an increase in the number of strains recovered and an increase in the relative numbers of the bacilli in each throat The highest prevalence was found one month after the epidemic had reached its height In Labrador, a similar increase was coincident with an epidemic of tracheitis During normal periods, the majority of the Pfeiffer strains were of the para nonindol-forming type During epidemic periods, the strains recovered were largely true indol-forming *B. Pfeifferi* Hemolytic streptococci were rarely found in normal persons During disease prevalence periods, they appeared in a small number of persons In Alabama, indifferent streptococci resembled the hemolytic streptococci in their distribution In Labrador, they were found to be widely distributed in both health and disease and composed apparently a part of the normal flora Green streptococci were found to be widely distributed in fairly large numbers in healthy as well as in sick people Intermediates, or organisms midway between green streptococci and pneumococci, were found in moderate numbers in each series of persons studied Early in the Alabama epidemic, they were present in large numbers in nearly all persons Pneumococci were not found in Alabama in normal persons The epidemic of colds in Alabama was accompanied by a marked increase in the incidence of these organisms In Labrador, pneumococci seemed to be part of the normal flora as they were generally distributed throughout the community, in many instances comprising a large proportion of the flora of an individual's throat The Labrador strains of pneumococci were avirulent A variety of other organisms such as diphtheroids, gram-negative rods and gram-positive cocci were found in small numbers in many persons both in health and disease

AUTHORS' SUMMARY

INFECTION OF MAN WITH BRUCELLA ABORTUS T. WEIGMAN, Arch f Hyg
102 77, 1929

Of thirty-eight patients with undulant fever, seventeen gave a history of contact with cows that had aborted and twelve stated that they drank raw milk In most of the cases there was a parallelism between the results of serologic examination and the clinical symptoms The author demonstrated that undulant fever developed in guinea-pigs not only following the peroral administration of milk from infected cows but also following its introduction through the scarified skin by means of inoculation He believes, however, that in man the great majority of cases of undulant fever are caused by drinking infected milk

IS THE BACTERIUM GRANULOSIS OF NOGUCHI THE CAUSE OF TRACHOMA?
K. LINDNER Arch f Ophth 122 391, 1929

Dr Lindner came to America in the summer of 1928 and examined Noguchi's monkeys at the Rockefeller Institute as well as many of the pupils at the school for American Indians in Albuquerque who are suffering from trachoma, including those from whom Noguchi had obtained his material for bacteriologic study

After seeing the eyes of the monkeys Lindner came to the conclusion that these experimentally produced conditions have nothing in common with trachoma He considers trachoma to be an inflammation of the conjunctiva of long duration which in every case leads to a thickening at least of the conjunctiva But in Noguchi's monkeys "the conjunctiva itself was normal in every case, delicate throughout and transparent, even after the disease had lasted a long time and there had been an increase in the number of follicles The lymphatic tissue of the conjunctiva alone was simultaneously diseased" He "found no trace of cicatrization in any of the animals demonstrated to me, aside from scars resulting from excision of the conjunctiva The conjunctival disease produced by Noguchi differs from that which we know of the beginning and course of experimental trachoma In none of Noguchi's animals were there an immediate, general inflammation of the conjunctiva with purulent secretion, such as has been noted

by many observers Inoculation with *B. granulosis* on the other hand, leads at first to a local inflammation at the site of inoculation. There the first granulations appear, they spread over the conjunctiva only as a secondary manifestation

" The Noguchi bacillus is found only in the subepithelial tissue not at the conjunctival surface, whereas the trachoma virus can always be found in the secretion also. Noguchi remarks that the follicles formed lie as if in capsules that is, sharply delimited, this in an animal 37 days after infection. In trachoma such an encapsulation at the beginning of the disease is never observed. It corresponds, moreover, to the clinical picture of folliculosis.

From the impression the author received of the condition in the eyes of the monkeys he expected to find no true trachoma among the school children whom Noguchi had studied in Albuquerque. On the contrary, a large proportion of the children examined showed a typical trachoma, and the inclusion bodies of von Prowazek could be demonstrated. Of the three persons of the four from whom Noguchi obtained the material for inoculation one was without signs of trachoma but two were definitely trachomatous, in the third stage.

The author points out the fact that many experimenters have found *Macacus rhesus* to be highly resistant to inoculations with material from trachomatous eyes, the orang-utang more suitable. But Noguchi had little success with orang-utangs. The author concludes that Noguchi has not isolated the cause of trachoma, but has probably found the agent or one of the agents of folliculosis.

CHARLES WEISS

EXPERIMENTAL INVESTIGATION OF POSTVACCINAL ENCEPHALITIS E. BERGER, Centralbl f Bakteriol 110 138, 1929

Berger attempts to test in rabbits certain ideas as to the relationship between vaccination and postvaccinal encephalitis but all of his experiments yielded negative results and failed to substantiate any of the theories tested.

PALL R. CANNON

THE SPIROCHETE CONTENT OF THE CORNEA AFTER SUBSCROTAL SYPHILIS INOCULATION SHIGERU INO Klin Wchnschr 8.2193, 1929

The cornea like the lymph nodes in rabbits with scrotal infection, is a spirochetes reservoir, even when inflammatory reactions are absent. Arsphenamine in the usual doses kills the spirochetes.

AUTHORS SUMMARY

Immunology

THE PRODUCTION OF ALLERGIC INFLAMMATION IN THE KIDNEYS OPAL E. HEPLER and J. P. SIMONDS Am J Path 5 473, 1929

Hemorrhage was found in the kidneys of every animal into which injections had been made if the animal was killed within seventy-two hours. Necrosis was observed in kidneys of sensitized rabbits only. Anaphylactic inflammation differs from other inflammation in the intensity and rapidity with which it occurs. This anaphylactic inflammation was caused by the direct toxic effect of the antigen on the sensitized tissues.

AUTHORS CONCLUSIONS

CHEMO-IMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS W. F. GOEBEL and O. T. AVERY, J Exper Med 50 521, 533, 1929

The synthesis of *p*-aminophenol β -glucoside and *p*-aminophenol β -galactoside has been described. These hexosides have been coupled to serum globulin. Two protein sugar complexes with different optical properties have been obtained.

When two chemically different carbohydrate derivatives are bound to the same protein, the newly formed antigens exhibit distinct immunologic specificity. When the same carbohydrate radical is conjugated with two chemically different and serologically distinct proteins, both of the sugar-proteins thus formed acquire a common serologic specificity. The newly acquired specificity of the artificially prepared sugar-proteins is determined by the chemical constitution of the carbohydrate radical attached to the protein molecules. Simple differences in the molecular configuration of the two isomers—dextrose and galactose—suffice to orientate protein specificity when the corresponding glucosides of the two sugars are coupled to the same protein. The unconjugated glucosides, although themselves not precipitable in immune serum, inhibit the reaction between the homologous sugar-protein and its specific antibody. The inhibition test is specific. The sugar derivatives unattached to protein exhibit the properties of carbohydrate haptens, they are nonantigenic but specifically reactive, as shown by inhibition tests, with antibodies induced by proteins containing the homologous diazotized glucoside. The specificity of artificially prepared sugar-proteins is discussed with reference to the chemo-immunologic nature of the bacterial antigens containing complex sugars.

AUTHORS' SUMMARY

ACTIVE AND PASSIVE ANAPHYLAXIS WITH SYNTHETIC SUGAR-PROTEINS

W S TILLET, O T AVERY and W F GOEBEL, *J Exper Med* **50** 551, 1929

Guinea-pigs passively sensitized with the serum of rabbits immunized with an artificially prepared sugar-protein (glucoglobulin) exhibit typical anaphylactic shock when subsequently inoculated with gluco-albumin, the serum of rabbits immunized with a second synthetic sugar-protein (galactoglobulin) similarly sensitizes guinea-pigs to galacto-albumin. The reactions in each instance are specific and depend for their specificity on the carbohydrate component, and not on the protein fraction of the synthesized sugar-protein. Guinea-pigs actively sensitized with gluco-globulin or galacto-globulin are similarly subject to anaphylactic shock when, after twenty-one days, they are given injections of sugar-proteins containing carbohydrate identical with that present in the sensitizing antigen, regardless of the kind of protein with which it is combined. The unconjugated glucosides, although themselves not capable of inducing shock, inhibit the anaphylactic reaction when injected immediately prior to the introduction of the toxigenic sugar-protein. The protective action of the glucosides disappears within two hours after injection. In order to elicit the phenomenon, the carbohydrate must be the same as that combined in the sugar-protein complex. Anaphylactic shock may be induced by uncombined globulin in guinea-pigs passively sensitized with either antigluco-globulin serum or antigalacto-globulin serum, globulin is similarly effective in animals actively sensitized with glucoglobulin or galactoglobulin. The reactions elicited by globulin alone are dependent on the common protein present in the antigens, and exhibit only species specificity.

AUTHORS' SUMMARY

ACTIVE IMMUNIZATION OF MICE AGAINST TYPE II PNEUMOCOCCI BY VACCINATION WITH YEAST

J Y SUGG, L V RICHARDSON and J M NEILL, *J Exper Med* **50** 579, 1929

Mice vaccinated with yeast were protected against subsequent infection with type II pneumococci, but not against types I or III. While the protection was not universal, as high a percentage of mice acquired active anti-type II immunity, as was obtained by vaccination of another group of mice with type II pneumococci. This specific protection of mice by active immunization with the yeast antigen, is probably due to the same immunologic relationship responsible for the anti-type II reactivity of the antisera of rabbits immunized with yeast antigen.

AUTHORS' SUMMARY

A STUDY OF VACCINAL IMMUNITY IN TISSUE CULTURES T M RIVERS, E HAAGEN and R S MUCKENFUSS, J Exper Med **50** 673, 1929

Normal corneas inoculated in vitro with vaccine virus and then cultivated in antivaccinal plasma developed typical vaccinal lesions associated with Guarneri's bodies. In such cultures, after an incubation period of twenty-four or forty-eight hours, active vaccine virus was demonstrated by means of appropriate methods. Immune corneas inoculated in vitro with vaccine virus and then cultivated in normal or in antivaccinal plasma revealed either mild vaccinal lesions or none at all. In some of the cultures after twenty-four and forty-eight hours of incubation, active vaccine virus was demonstrated.

AUTHORS' SUMMARY

CUTANEOUS REACTIONS TO THE POLYSACCHARIDES AND PROTEINS OF PNEUMOCOCCUS IN LOBAR PNEUMONIA W S TILLETT and T FRANCIS, JR, J Exper Med **50** 687, 1929

Pneumococcus polysaccharides, when injected intradermally into patients convalescent from pneumonia, are capable of eliciting a response. The polysaccharide inducing a cutaneous reaction was found always to be homologous in type to that of the pneumococcus causing the infection. The character of the reaction incited by the protein-free bacterial sugars is of the immediate wheal and erythema type. A patient's capacity to react was found to be intimately associated both with recovery from infection and with the presence of type specific antibodies in the circulating blood. The so-called nucleoprotein of pneumococcus, when injected intradermally, also causes a local cutaneous reaction in patients during convalescence from lobar pneumonia. The local lesion resulting from the injection of protein is tuberculin-like and differs from that evoked by the type-specific polysaccharides in gross appearance, time of development and duration. Persons who are acutely ill with and convalescent from pneumococcus pneumonia possess in their circulating blood precipitins that are reactive with pneumococcus protein. In the observations recorded, the concentration of antiprotein antibodies in the blood serum did not seem to influence the patient's capacity to react to intradermal injection of the protein.

AUTHORS' SUMMARY

A PRECIPITIN TEST IN EXPERIMENTAL TRICHINIASIS GEORGE W BACHMAN, J Prev Med **3** 465, 1929

The present work corroborates the previous conclusions that precipitins can be demonstrated in the serums of rabbits infected with *Trichinella spiralis* from twenty to thirty days after infection, when one uses an antigen prepared from isolated larvae dried, ground and extracted with 0.01 normal hydrochloric acid in 0.85 per cent sodium chloride. A comparative study of the results with this acid antigen and with another antigen prepared with Coca's solution (768 precipitation tests on twenty rabbits) showed that the latter was the more potent, precipitin antibodies being detected in from five to twenty days after infection. When using the antigen prepared with Coca's solution, it is thus possible to detect the infection during the period of ingress, that is, while the adult worms are still in the small intestine and before the larvae have entered the blood stream.

AUTHOR'S SUMMARY

COMPLEMENT FIXATION IN EXPERIMENTAL TRICHINIASIS GEORGE W BACHMAN and PARIS E MENENDEZ, J Prev Med **3** 471, 1929

The titers of eight *Trichinella* infested rabbits, on which 150 complement-fixation tests were run, rose on the third day after infection and then dropped from the fifteenth to twentieth day after infection. From the twenty-fifth day to the thirty-fifth (the end of the experiment) the titer increased very rapidly. Due to the great variability in the titer and the nonspecific reaction of the serum

of rabbits, it is questionable whether the test is practicable until the twenty-fifth day of infection, at which time the antibody formation is of such a concentration as to over-rule the nonspecific action of the serum

AUTHORS' SUMMARY

THE SEROLOGICAL RELATIONSHIPS OF TWENTY-SIX STRAINS OF PASTEURELLA
J T CORNELIUS, J Path & Bact **32** 355, 1929

It has been possible by means of agglutinin-absorption tests to group seventeen *Pasteurella* strains out of twenty-six, group I containing seven, group II five, group III three and group IV two strains, the remaining nine strains defied classification. Complement-fixation tests carried out with two group I strains and a number of serums partially confirmed this grouping. No relationship between the serologic group and the animal origin of the strains was evident.

AUTHOR'S SUMMARY

THE PASSAGE OF ANTIBODIES INTO THE AQUEOUS HUMOUR AND ITS REACTION
TO THE FORM OF THE SOLUTION. A. FRANCESCHETTI and C. HALLAUER,
Arch f Augenh **100-101** 81, 1929

Although the permeability of the aqueous humor for antibodies is increased by the effect of diuretics, the passage of substances into the media of the eye is controlled not only by the condition of the "filter" (the aqueous humor barrier) but also by the physicochemical condition of the permeating substance. The authors have tested this fact, using plasma, serum and serum albumin fractions.

In rabbits, the antibody (agglutinin) passes into the aqueous humor more easily when it is in the form of a serum globulin than in the form of native, unaltered serum injected intravenously. There is no difference in the transfer of antibody-containing euglobin and antibody-containing pseudoglobulin (from the same homologous immune serum) as regards the ease with which the passage is made.

CHARLES WEISS

IMMUNIZATION AGAINST TUBERCULOSIS BY MEANS OF BCG. BELONOWSKI,
Centralbl f Bakteriologie **110** 184, 1929

Belonowski, in tissue cultures of human lymphocytes, tested their reaction to virulent tubercle bacilli and to BCG. A colored plate illustrates his observations, namely, that with virulent tubercle bacilli there is quickly a marked necrosis of the cells with death of the culture. At times the development of tubercles, with caseous necrosis, giant cells, etc., is observed, but usually the cultures die rapidly. With BCG, however, the cells develop well and the majority of the lymphocytes become epithelioid cells, these remain intact and show a vigorous phagocytosis, the phagocytosed microbes losing their shape and apparently being digested. Furthermore, cultures of lymphocytes after having been in contact with BCG for twenty-four hours seem to acquire some immunity to virulent tubercle bacilli in that they are not so quickly injured by the latter as they are without this previous treatment.

PAUL R. CANNON

THE RETICULO-ENDOTHELIAL SYSTEM AND IMMUNITY. BIELING, Centralbl f
Bakteriologie **110** 195, 1929

This paper, with seven colored figures, consists of a general discussion of the distribution and significance of the reticulo-endothelial system with reference to its role in resistance to infectious disease. The newer experimental investigations are summarized and discussed, particularly the problem of blockade. The author concludes that immunity should be considered as a property of the entire organism and that the old strife as to the relative importance of humoral and cellular elements is of no great importance as the immune process depends on both.

PAUL R. CANNON

SYPHILIS IMMUNITY AND SYMPTOMLESS SYPHILITIC SUPERINFECTION R
PRIGGE and E V RUTKOWSKI, Deutsche med Wchnschr 55.1508, 1929

Material from a left inguinal lymph node removed from an untreated patient with paresis did not produce syphilis when injected into rabbits. The right thigh of this patient was scarified and inoculated with material from a syphilitic lesion of a rabbit containing spirochetes with considerable virulence for rabbits. No symptoms resulted from this and the skin healed rapidly. Ninety-three days later four mice were inoculated with material from a lymph node removed from the right groin. The mice were killed after being perfectly well for a year, and material from the axillary and inguinal lymph nodes and the brain was inoculated into the scrotum and testes of four rabbits. Three of the four rabbits developed lesions in which spirochetes were demonstrated. The authors conclude that immunity in syphilis may be only a false immunity which while it inhibits chancre formation in a reinfection, does not protect against the penetration of virulent spirochetes into the lymph nodes and other tissues of the body.

PAUL J BRESLICH

PROTECTIVE INOCULATION OF CATTLE AGAINST BOVINE TUBERCULOSIS WITH
SLIGHTLY VIRULENT BOVINE TUBERCLE BACILLI UHLENHUTH, A
MÜLLER and K. HILLENBRANDT Deutsche med Wchnschr 55 1535 1929

Cattle from 4 to 6 months old with negative tuberculin reactions were divided into four groups of six each. The first group was inoculated subcutaneously with 100 mg of BCG and the second group with 100 mg of an old culture of bovine tubercle bacilli grown on artificial mediums since 1902. This culture inoculated into guinea-pigs produced a form of tuberculosis which usually healed in nine months. The third group of cattle received 1 Gm of the avirulent culture intraperitoneally while the fourth group received none. After from one to three months all the animals were placed with cattle known to have tuberculosis of the lungs and with tubercle bacilli in the sputum. At postmortem examination of these four groups of cattle it was found that two in each of the first three groups had no tuberculosis while all of the uninoculated control animals were infected. The authors think it highly improbable that the inoculations produced any effective immunity against tuberculosis in these cattle.

PAUL J BRESLICH

SPONTANEOUSLY HEALED DIPHTHERIA FRANZ HAMBURGER and J SIEGL,
München med Wchnschr 76 1537 1929

Among twenty patients whose mild forms of diphtheria had been allowed to heal without injections of antitoxin fifteen gave positive Schick reactions a short time after convalescence. These results indicate that free antitoxin is not demonstrable in a large number of patients with spontaneously healed diphtheria.

EDWIN F HIRSCH

IMMUNIZATION OF MAN WITH HUMAN BLOOD O THOMSEN Ugesk f laeger
91 776 1929

The results tend to indicate that blood of one type has no antigenic power in persons of other types and that it is rather doubtful whether the differentiation into type rests on an antigenic basis.

Tumors

TUBERCULOSIS AND MALIGNANT TUMOR LEO V SCHNEIDER Am Rev Tuberc
20 271, 1929

Active progressive tuberculosis associated with any form of malignant tumor is rather uncommon. It is difficult to demonstrate tubercle bacilli in the sputum of patients suffering from both tuberculosis and malignant growth. Sputum should

be examined repeatedly. The coexistence of pulmonary tuberculosis and malignant tumor is extremely rare before the age of 35

H J CORPER

OSTEITIS FIBROSA AND GIANT CELL TUMOR C F GESCHICKTLER, M M COPELAND and J C BLOODGOOD, Arch Surg **19** 169, 1929

There is a foreword by Dr Bloodgood. This is an extensive article covering lesions of bones ranging from bone cysts to giant cell tumors and epulis and xanthomas of the tendons. Over 400 lesions were studied, and from their studies the authors conclude that osteitis fibrosa, osteitis cystica, bone cysts of various types, giant cell tumors, xanthoma tumors and epulis all bear a genetic relationship to each other. They feel that the cystic lesions result from healing processes occurring in the giant cell tumor, and were able to demonstrate several transitional lesions. The part played by the osteoclasts is stressed, in that they feel they can demonstrate that these cells play a role in the transition process changing the bone by canalizing it and stimulating blood vessel formation. This transition occurs chiefly in calcified cartilage, as seen in the epiphyseal regions and in the cartilaginous centers of the flat bones. The same applies to epulis, where there are temporary calcified structures at the roots of the teeth, and in xanthomas of the tendon sheaths they find that these occur in association with the sesamoid bones. They view all these lesions as neoplasms and stress the importance of trauma in their etiology, maintaining, however, that there is a primary proliferation not inflammatory in origin.

N E ZILK

THE INFLUENCE OF DILUTION ON THE CARCINOGENIC EFFECT OF TAR I HIEGER, J Path & Bact **32** 419, 1929

A carcinogenic agent (ether extract of tar) was tested on mice in three concentrations, namely in the undiluted state (100 per cent concentration) and in 10 and 1 per cent dilutions of this. The reduction in strength from 100 to 10 per cent delayed the earliest appearance, but did not lessen the total yield of tumors or the average induction period. On the other hand, the diminution from 10 to 1 per cent, while prolonging the induction period, has reduced the production of tumors to an extremely low total. Hence the experiment shows that an increase in concentration of the carcinogenic agent beyond a certain point does not increase the number of tumors.

AUTHOR'S SUMMARY

THE MODIFYING INFLUENCE OF DICHLOROETHYL SULPHIDE ON THE INDUCTION OF TUMOURS IN MICE BY TAR I BERENBLUM, J Path & Bact **32** 425, 1929

The addition of 0.1 per cent mustard gas to a carcinogenic tar inhibits the tar from inducing tumors. This anticarcinogenic effect of mustard gas is due to its action on the animal, so that the skin no longer responds to a carcinogenic tar. The induction of warts is still inhibited if the mustard gas is added to the tar as late as the eleventh week of tarring.

AUTHOR'S SUMMARY

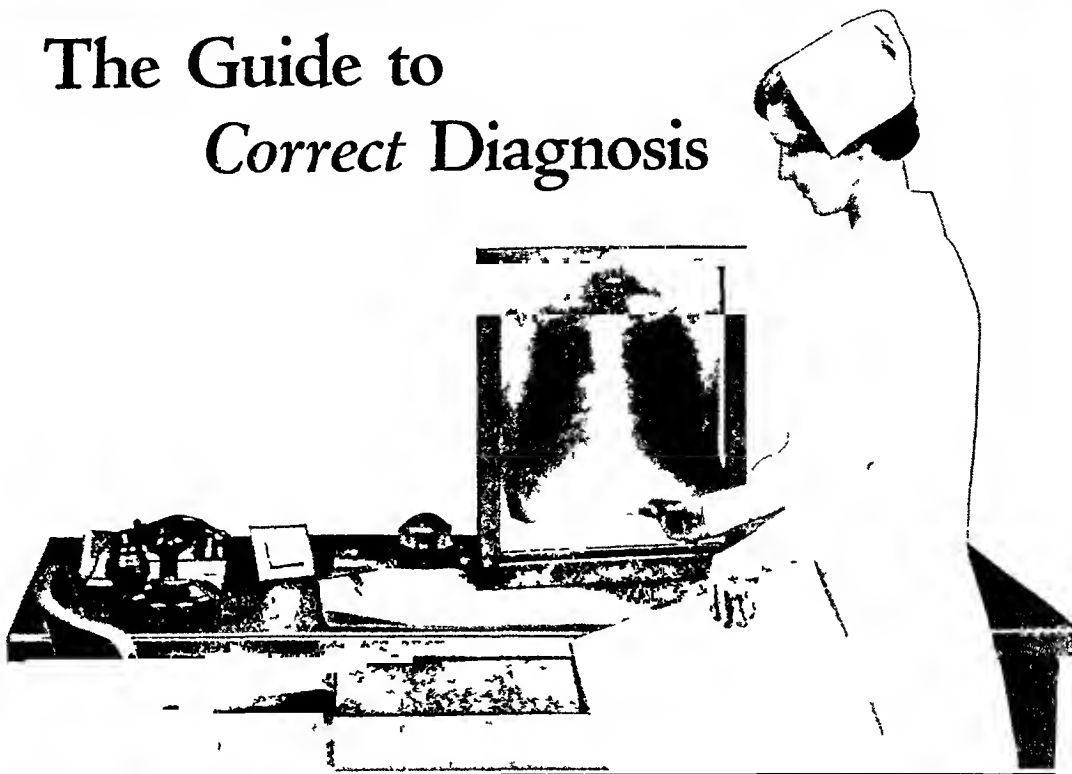
SEROLOGIC SPECIFICITY OF CARCINOMA CELLS L HIRSZFELD, W HALBER and J LASKOWSKI, Klin Wchnschr **8** 1563, 1929

The results of the experiments recorded indicate that many carcinomas, especially gastric, contain lipid of special serologic character.

THE SIGNIFICANCE OF ALKALINE REACTION IN THE GROWTH OF CARCINOMA J FLASZEN and H WACHTEL, Klin Wchnschr **8** 1912, 1929

Carcinomatous tissues of the mouse suspended in 0.1 per cent sodium bicarbonate, 0.1 per cent sodium hydroxide or 0.1 per cent ammonia solution and injected into

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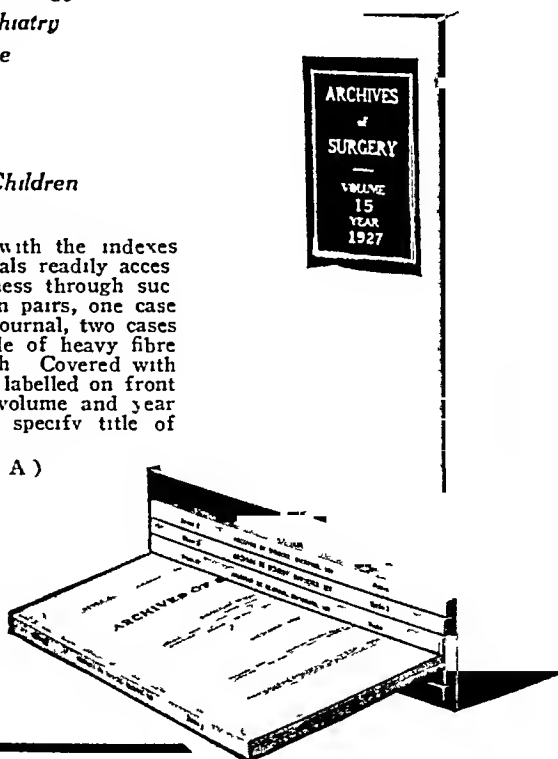
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PHILADELPHIA PATHOLOGICAL SOCIETY

Dec 12, 1929

J HAROLD AUSTIN, *Presiding*

VESICOVAGINAL AND RECTOVAGINAL FISTULAS FOLLOWING APPLICATION OF RADIUM FOR RECURRENT CARCINOMA OF THE VAGINAL VAULT, WITH FROM UREMIA LEWIS C SCHEFFER

The autopsy specimens were exhibited from a woman, aged 41 at the time of death in 1928. In 1914 she had had a right salpingo-oophorectomy, and in 1921 a vaginal hysterectomy for squamous cell carcinoma of the cervix. Six weeks after hysterectomy, a recurrence was discovered in the vaginal vault, and a local application of 100 mg of radium was made for twenty-four hours. Soon after this, vesicovaginal and rectovaginal fistulas developed which persisted. Two months prior to the final admission she developed pain in the left flank, fever, nausea and vomiting. On admission, the patient had some of the manifestations of intestinal obstruction, but soon a diagnosis of uremia was established. Convulsions followed and death occurred in twenty-four hours.

At autopsy, no metastases or any evidences of carcinoma were found. The right kidney showed hydronephrosis, the right ureter being thickened and obliterated near its entrance to the bladder. The left kidney showed pyonephrosis, accompanied by a greatly thickened but patent ureter exuding pus. The bladder contained fecal material, as the vesicovaginal fistula was in close proximity to the rectovaginal one.

Striking features of this case were the massive destruction of the kidney following infection of the bladder and entire urinary tract after the production of the fistulas, the prolongation of life for nearly seven years in the presence of such infection, the absence of recurrent carcinoma, either gross or microscopic, in the vagina, pelvis or abdomen.

A RAPID METHOD FOR THE PREPARATION OF PARAFFIN SECTIONS B L CRAWFORD

This method is particularly applicable to examination of small pieces of tissue removed for biopsy, when frozen section method is not applicable. The method may be completed within from six to twenty-four hours as necessary. If desired, serial sections may be cut and many examined from various levels of the tissue, thus affording adequate material for a careful study from which to submit a reliable histologic report.

1 Place small pieces of tissue, not more than 2 mm thick, for one-half hour or longer in "alcoholic formol" (Lavdowsky Anat Hefte 4 361, 1894)

Alcohol (95 per cent)	20 parts
Formol	6 parts
Acetic acid	1 part
Water	40 parts

2 Dehydrate in acetone, making three changes to pure acetone each time, three fourths of an hour each

3 Clear in benzene fifteen minutes or longer until tissue is transparent

4 Infiltrate in fresh paraffin one hour or longer

5 Block cut, mount and stain in the usual way

CULTURE VERSUS GUINEA-PIG INOCULATION FOR IDENTIFICATION OF THE TUBERCLE BACILLUS C J BUCHER

The methods usually employed in the diagnosis of tuberculosis, are a search for acid-fast bacilli in stained smears and the inoculation of guinea-pigs, in the hope that the disease may be reproduced in the animal.

These methods, while useful, have certain objections. Even with the most careful search, tubercle bacilli are often not found in smears. Inoculated animals often die of infections from extraneous sources or of those carried by contaminants in the inoculated material. Moreover, accidental infection of guinea-pigs with *Bacillus tuberculosis* has been recorded (Sewall), and certain German investigators believe that some strains of human tubercle bacilli are not pathogenic for guinea-pigs.

In an effort to find a more reliable and economical method to supplant guinea-pig inoculation in the identification of the tubercle bacillus, and one which at the same time would be free from intricate technicalities I have employed the method of Corper and Uvel for the cultivation of the bacillus directly from suspected material.

Seventy-two cultures were made from pathologic material, some known to contain tubercle bacilli and some in which there was no substantial evidence that the organisms were present. This material included sputum, urine, feces, spinal fluid, pleural fluid, pus aspirated from a bronchus, pus from a cold abscess and human tissue. Stained smears of all specimens were examined microscopically. Portions of forty-two of them were inoculated into guinea-pigs. Twenty-two of the seventy-two cultures examined were positive for *Bacillus tuberculosis*. Ten of these represented material, a portion of which had been inoculated into guinea-pigs. Of these, a positive culture was obtained twice with negative results in the animals, and once a negative culture was obtained while the inoculated animal developed tuberculosis. The failure to obtain a positive culture in the last instance was due to the growth of a mold on the culture medium.

The method is as reliable as the older methods, it is simple as far as technical details are concerned, and it is more economical than guinea-pig inoculation.

THE DIFFUSIBILITY OF CALCIUM IN ALLERGIC DISORDERS A CANTAROW

Previously reported investigations of calcium balance in allergic disorders have concerned themselves with the determination of total serum calcium and of calcium intake and output. These studies have, in the great majority of instances, revealed no deviation from the normal and have led to the belief that no demonstrable disturbance of calcium metabolism exists in these conditions. Since the work of Rona and Takahashi, establishing the partition of serum calcium into diffusible and nondiffusible fractions, considerable evidence has accumulated to indicate that the physiologic activity of calcium is dependent on the various forms in which it exists. A disturbance of the ratio between the diffusible and nondiffusible fractions may occur, with distinct physiologic effects, without any alteration in the level of total serum calcium.

The present study consists of the determination of the diffusibility of calcium in twenty-five patients with bronchial asthma, three with mucous colitis, two with vasomotor rhinitis, one with angioneurotic edema and sixty-three with pulmonary tuberculosis. The method employed consists in the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case. The spinal fluid calcium is termed "diffusible," although "diffused" is probably more correct. The difference between this figure and the total serum calcium is the nondiffusible portion.

The observations appear to indicate that in bronchial asthma and allied disorders there is a definite and constant disturbance of calcium balance in the form of an increase in the ratio of diffusible to nondiffusible calcium. It is conceivable that this observation is related in some way to the increased cellular permeability which is believed to exist in these conditions.

In chronic pulmonary tuberculosis there is considerable variation in the diffusibility of calcium. It seems that an increased diffusibility ratio is associated with an exudative type of lesion with a high degree of clinical activity, while a decreased diffusibility ratio is associated with a productive process, relatively benign clinically. Whether or not these observations bear any relation to the problem of allergy in tuberculosis cannot be stated definitely.

THE EXPERIMENTAL PRODUCTION OF CHRONIC FOCI OF INFECTION V H MOON

The methods commonly used for infecting animals in order to determine the pathogenicity of bacteria are inadequate in many instances. Frequently the inoculated animals either succumb or recover promptly, and the procedure does not approximate the conditions present in disease in man. A new method for producing chronic foci of infection has been developed in the Department of Pathology of Jefferson Medical College.

Applicators of cotton, similar to those commonly used for throat swabs, are made on no. 20 or no. 22 rustless wire rather than on wood. The cotton is wound rather loosely so that moderate force will slip it off the wire. A trocar and cannula are inserted into the region to be inoculated. The trocar is then withdrawn leaving the cannula in place. The cotton applicator is dipped into the material to be inoculated and is inserted through the cannula. The swab is pushed beyond the end of the cannula, then, on withdrawing the wire, the end of the cannula pushes off the cotton into the tissue or cavity desired to be infected. The cannula is then withdrawn.

The method is merely a simplified procedure for implanting infection in a porous foreign substance within the tissues. The foreign substance serves to maintain the infection against effective body resistance. The method is well suited for producing chronic foci in subcutaneous and intramuscular areas and in the body cavities. By exposing the abdominal viscera the infection may be implanted easily in the spleen, liver, gallbladder or other structures. In such instances, a smaller cannula and correspondingly smaller applicators are used. For small animals a spinal puncture needle of large size makes a suitable cannula. The cotton swab, on fine stiff wire, is wound small enough to pass readily through the lumen of the needle.

Dogs are so resistant to ordinary inoculations that they are seldom used for the purpose. They are well adapted to this method. When inoculated with streptococci, masses of inflammatory granulations, from 3 to 5 cm in diameter, develop in a few weeks. The organism is regularly recovered from the area inoculated and frequently from the blood and from the substance of other organs. Hemolytic streptococci and *S. viridans* are recovered in pure culture after six months' implantation.

The organic changes produced in young dogs and rabbits include acute nephritis, endocarditis, arthritis, infarcts, splenic atrophy and fibrosis, periportal inflammation in the liver, lymphadenitis, etc. Detailed results will be given later.

Regular Meeting, Jan. 9, 1930

J. HAROLD AUSTIN, *President*

THE EFFECT OF HIGH FREQUENCY SOUND WAVES ON CELLS AND TISSUES E. NEWTON HARVEY, Professor of Physiology, Princeton University

When a quartz crystal, cut in a certain plane, is compressed, it becomes charged positively on one side and negatively on the other, the piezo-electric effect. Conversely, if a quartz crystal is charged positive on one side and negative on the other, it will compress. Reversing the charges causes expansion. If the reversing

of the charges is carried out rapidly by an oscillating electric field, sound waves of a frequency corresponding to the frequency of the oscillating field will be produced, which travel through a medium in contact with the crystal Wood and Loomis (*Philosophical Magazine* 4 417, 1927) have described a high power (2 kilowatt) oscillator and Harvey and Loomis (*Nature* 121 622, 1928) a low power (75 watt) oscillator and crystal for use on the microscope Frequencies of 300 to 2,500 kilocycles have been employed by the author in collaboration with Mr A L Loomis to study effects on living cells The sound waves cannot be heard, but have definite mechanical effects A drop of water is broken into a fine mist Elodea cells show rapid whirling of the chloroplasts and breaking up of these bodies and the plasma membrane Blood corpuscles are laked, provided they are not thrown into nodes of standing waves Egg cells and infusoria are cytolized, and the more easily the larger the cells Bacteria can be broken up by high intensity sound waves and the suspension sterilized, but complete destruction takes a long time Skeletal muscle, nerve and luminous cells are not readily stimulated Quiescent isolated turtle and frog ventricle can be made to beat with regular rhythm Beating auricles will beat more rapidly Small fish can be killed, and the cause of death appears to be hemolysis and rupture of gill membranes From the stirring of cell contents, conclusions can sometimes be drawn regarding the viscosity of cells No difference in effect can be detected with different frequencies None of the effects mentioned are due to heating of the cells or to electric influences in the high frequency field The cytolysis of cells has been shown by Johnson (*J Physiol* 67 356, 1929) to result from the cavitation or removal of dissolved gases from solution In gas free solutions or solutions under pressure, cells are unharmed

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Dec 23, 1929

HARRISON S MARTLAND, President

ADENOFIBROSARCOMA OF THE BREAST LAWRENCE SOPHIAN (by invitation)

This is a survey of sarcomas of the breast, undertaken with the object of differentiating the group that may be traced through a stage in which epithelial elements are present The stimulus for this study arose in the accidental finding of a case of tumor of the breast in which the histologic observations were similar to those in the ordinary adenofibroma with the exception that the fibroblastic tissue was actively growing in the form of a fibrosarcoma Attempts to find authority for giving the prognosis in such a case made it apparent that no data were available Subsequently a similar case came to hand In addition, the cases of fibrosarcoma of the breast to be found in the files of the Huntington Hospital in Boston were reexamined with regard to the histologic observations and clinical course of the tumor A grouping was made, separating those tumors in which there was an admixture of epithelial elements such as glands or ducts from those in which the tumor was entirely composed of fibroblasts Of the total of fifteen cases, seven cases including the two personally seen were found to present features which justified the first diagnosis, namely, "adenofibrosarcoma"

Comparison with other statistics is not justified because of the small number of cases here reported, but in general it may be noted that Ewing states that true adenosarcoma of the breast is rare, while Deaver and MacFarland give a total of 193 cases of adenosarcoma in a group of 838 sarcomas of the breast S W Gross compiled a series of 156 cases of sarcomas of which 33 per cent were termed "adenoid" The most recent compilation is that of Finsterer Here the terminology must be interpreted, but of forty cases the eighteen which he called "cystosarcoma" might be considered of the type with which the present study is concerned

Illustrations are appended to demonstrate the activity that is readily apparent in the tumors classified as "adenofibrosarcoma." Mitotic figures are numerous. The cells are frequently anaplastic and the tumor capsules show invasion in many sections. The clinical course in the two groups was compared. Of seven cases in which the diagnosis was "adenofibrosarcoma," five were free from disease when the last reports were received, after periods ranging from six months to seven years. One case had a recurrence four and one-half years after the first operation. The recurrent tumor was histologically "pure fibrosarcoma." The last case showed only a trace of epithelial structure when first seen. Rapid fibroblastic proliferation and two recurrences took place, and death occurred a year after operation. In the second group in which the diagnosis was "fibrosarcoma," the subsequent course remains unknown in four of eight cases. Three of the remaining four patients died with recurrence of metastases within eight months following operation. In the fourth case, which was histologically of low malignancy, the patient was free from disease six years after the operation.

In Finsterer's series the group in which the diagnosis was "cystosarcoma" showed the following clinical course. Of eighteen patients, twelve remained free from disease, one showed recurrence and five died of intercurrent diseases, there were no metastases. Finsterer contrasted these with his group of twenty-one cases of round cell and spindle cell sarcoma, in which only five were free from disease, nine showed recurrences, three showed metastases and the remainder were not followed.

From the present group and that reported by Finsterer one is led to conclude that the prognosis in sarcoma of the breast does not depend entirely on the ordinary criteria of cell activity, but also on the type of tumor, especially with regard to the presence of epithelial elements. In those cases in which epithelial lined clefts are found, metastasis is apparently rare, and there is a good chance for cure by local removal. In no case in either Finsterer's series or ours were there metastases to the regional lymph nodes either primarily or after operation, so that it seems unnecessary to perform a radical operation. I also feel that grouping cases in this way gives one an insight as to the biologic history of these tumors, in that the gradation from simple adenofibroma to more and more malignant sarcomas may be traced, adenofibrosarcoma being an intermediary form which may later on or on recurrence become converted into the most malignant form, the pure fibrosarcoma.

DISCUSSION

NICHOLAS ALTER. I think that the cancer campaign and modern surgery have helped us to reconstruct the stages of certain pathologic lesions like sarcoma of the breast, and to explain its histogenesis. We used to talk generally about spindle cell sarcoma of the breast. It was striking to me for a long time that many of the so-called sarcomas of the breast were well encapsulated. Now we get many of these tumors in the earlier stages. I had an opportunity not long ago to study a few cases in which the epithelial structures were very clear, and it is not impossible that all spindle cell sarcomas of the breast come from the innocent-looking intracanalicular fibro-adenoma. This remains encapsulated even when undergoing the more advanced stages of malignant transformation, until the sarcoma becomes extensive and the capsule is lost by the diffuse invasion of the surrounding tissues. In this case the epithelial structures may be quite obscure. These extensive sarcomas are now rare because the patients are operated on much sooner, and fortunately we see more of the early stages of the sarcomatous changes of the intracanalicular adenofibroma.

LAWRENCE SOPHIAN. I think that these tumors go through a series of changes beginning with adenofibroma, passing through the stage which we recognize as adenofibrosarcoma and then going on to pure fibrosarcoma, this is brought out by two of the cases which I reported, which went through these stages. A feature about these cases which may be important from the clinical point of view is that in no case of Finsterer's or of mine were the lymph glands the site of metastases,

no matter how malignant the tumor appeared, which shows that in these cases, the performance of a radical operation is unnecessary

HARRISON S MARTLAND Have any of these metastasized to the lungs?

LAWRENCE SOPHIAN Yes

HARRISON S MARTLAND They behave like osteogenic sarcoma, then

LARGE FIBROSARCOMA (?) IN THE PLEURA ANGILO M SALA

A colored woman, aged 40, was admitted to the Harlem Hospital with symptoms of intermittent pain in the right side of the chest and a sense of fulness of the throat, of three months' duration. A roentgen diagnosis was made of a tumor in the right pleural cavity, compressing the lung. There were no evidences of metastases.

At operation the pleura was found covering a tumor mass, which was hard and about the size of a coconut. The pleura was incised. A plane of cleavage was found between the tumor and the surrounding tissue, and the tumor was easily separated anteriorly and posteriorly, but it was firmly adherent at the diaphragmatic surface.

As the patient's condition suddenly became alarming, the operation was stopped. Death followed in an hour. Inspection and removal of the tumor were allowed, but a complete autopsy was refused.

The tumor was easily enucleated, but it was found adherent to the diaphragmatic surface by a broad pedicle. It weighed 1,765 Gm and was completely encapsulated. It grossly resembled a huge uterine fibroid.

The histologic picture seemed to be that of a fibrosarcoma. Although there were areas suggestive of endothelioma, the growth as a whole more closely resembled a neurogenic sarcoma. One could question whether the tumor arose from the pleura at all, it being an encapsulated growth, and not diffuse. If it was a fibrosarcoma, its rate of growth must have been exceedingly slow. This type of tumor, as a matter of fact, has been reported as developing for years. We have no way of knowing how long the tumor in question has been growing to attain its size. This type of tumor does not metastasize, and from this standpoint one might well call it a cellular fibroma rather than a fibrosarcoma.

DISCUSSION

HARRISON S MARTLAND How did the patient die?

A M SALA Of operative shock.

HARRISON S MARTLAND How did death occur in the other cases?

A M SALA From pressure symptoms.

ALFRED PLAUT Even without having seen the slides to which Dr Sala has referred, I do not think it is probable that this tumor is an endothelioma. The term "endothelioma" has been used or abused very much, but it is disappearing slowly from the literature. Some of you will remember Dr Klemperer's demonstration not very long ago, and my demonstration several years ago. The tumors probably originate from the lining cells of serous cavities. These cells have the power to develop epithelial structures on the one hand, and typical connective tissue structures on the other hand. In tissue cultures Maximow has succeeded in getting both forms from the lining cells. They are generally called mesothelioma, or celothelioma, which means the lining cells of a large cavity. Even if this slide should show pictures to indicate a connection between blood vessel cells and tumor cells, that would not induce me to call it an endothelioma when most of the tumors show a homogeneous structure without any arrangement characteristic of true endothelium.

A M SALA If we accept this tumor as a pleural tumor, Dr Plaut's contention is to the point, but then we might both be speaking of the same thing in different terms. The name mesothelioma is also a generic one, presumably sus-

ceptible of as much use and abuse as endothelioma. The concept of mesothelioma as outlined by Dr. Plaut still has to be accepted by many, and I personally have no definite opinion on the point.

ANEURYSM OF THE BRONCHIAL ARTERY ANGELO M. SALA

A colored man, aged 35, was admitted to the hospital in extremis and died in four hours. Autopsy disclosed an aneurysmal sac involving the bronchial and the first two intercostal arteries on the left side, and compressing the esophagus and trachea and the left stem bronchus at its origin. The syphilitic nature of the disease was proved histologically.

DISCUSSION

CHARLES NORRIS From the pictures shown I believe that it is an aneurysm of the ductus arteriosus.

E. LIBMAN There seem to be three distinct openings.

ANGELO M. SALA No ductus was found, and there were three distinct openings in the sac.

ANEURYSM OF AORTA RUPTURING INTO SUPERIOR VENA CAVA LAWRENCE H. COTTER

The case is presented because it is a typical one of aneurysm rupturing into the superior vena cava, with all the characteristic signs except pain.

A. R., aged 38, was admitted to Gouverneur Hospital on Aug. 30, 1929. The chief complaints were (1) cough and dyspnea, (2) swelling and dark discoloration of the face and neck, and (3) dizziness and headache. There was no past history of cardiac disease or syphilis. While boarding a truck, the patient was suddenly seized with a choking sensation and a cough. He felt a throbbing in his head and had a sensation of dizziness. Simultaneously a friend called his attention to the fact that his head, neck and hands were blue. He also had headache, but at no time had pain in the chest. These symptoms were present when the patient was admitted to the hospital two hours later.

On physical examination, the patient appeared acutely ill, he lay in bed in an orthopneic position, with marked respiratory distress. The head, neck, arms, hands and upper half of the trunk were swollen and cyanotic. The lower margin of the edema and cyanosis was about 2 cm. below the nipples, and the margin was rather sharp. Examination of the eyes showed the conjunctivae to be edematous and engorged, the retina showed marked engorgement of the veins and numerous small hemorrhages. The mucous membranes of the mouth were cyanotic. The heart showed apex impulse in the seventh interspace, anterior axillary line. There was dullness over the upper sternum and to the right and left. There was a loud systolic and a blowing diastolic murmur heard at the base of the heart and along the left sternal border. The pulses were Corrigan in type. The blood pressure in the right arm was 190 systolic and 0 diastolic, and in the left arm 175 systolic and 20 diastolic. The edge of the liver was 5 cm. below the costal margin. The Wassermann reaction of the blood was ++++. The red blood cells numbered 3,700,000 and the white blood cells 17,000. The nonprotein nitrogen was 128 mg. per hundred cubic centimeters. Roentgen examination showed an aneurysm of the aorta and cardiac hypertrophy. The temperature was 99, the pulse 120 and the respirations 24.

The clinical diagnosis was aortic insufficiency and aneurysm of the aorta with rupture into the superior vena cava. The specimen showed aortitis which involved the aortic valves, the ascending, transverse and descending aorta, with considerable dilatation. There was an old rupture about 3 cm. in diameter which is about 3 cm. above the aortic ring, a false sac had formed, the walls of which were made up of the superior vena cava and the aneurysmal sac. There was a fresh rupture about 1 cm. in diameter into the superior vena cava 5 cm. above the auricle.

It seems that the aneurysm of the aorta must have ruptured to form the false sac at some time previous without giving any symptoms

DISCUSSION

HARRISON S MARTLAND As I recall, Wayne Babcock recently advocated the surgical shunting off of the blood supply of an aneurysm into the veins of the neck That was almost done here, was it not?

LAWRENCE H COTTER Yes, in this case the patient lived for two days

CASE OF SCHILDER'S ENCEPHALITIS L W SMITH AND I SCHFIFER (by invitation)

An unusual case of Schilder's disease in a young Jew, aged 24, was presented The onset of the disease dated back probably eleven years, when he had an attack of grip, followed by pain in the lower part of the back and difficulty with locomotion The condition subsequently improved At the age of 20 he had an attack diagnosed as encephalitis, lasting about a month, when he developed muscular weakness with shakiness of the arms and hands This progressed steadily up to the present illness The mentality had apparently not been retarded and he had done well in his school work The present illness began three days before admission, with fibrillary spasm of the muscles on the right side of the face He had lost speech since this time and had apparently been unconscious at intervals

On physical examination the patient appeared emaciated, but otherwise fairly well developed He was having constant jacksonian convulsions, which involved chiefly the left arm and leg The eyes were staring, with the pupils unequal and nonreactive to light, with a slight horizontal nystagmus Between the convulsions the face presented a typical parkinsonian mask There was no rigidity of the neck, but both Kernig's and Babinski's reflexes were positive There was moderate spasticity of the extremities, with hyperactivity of the deep reflexes The spinal fluid was clear and under slightly increased pressure, with a normal cell count The patient became progressively worse, with a temperature of 104.8 F, and died in convulsions

The pathologic observations proved entirely negative, except for the central nervous system There was no definite atrophy, but the consistency of the brain in the region of the right motor cortex was diminished Coronal sections, after fixation, showed the typical gelatinous degeneration of the subcortical white matter in Schilder's disease This was most marked in the right frontal lobe, extending posteriorly to the parietal region, but disappearing in the occipital lobe Similar, but less extensive, changes of the frontal lobe were noted on the left side It was difficult to make out any gross changes in the cerebellar lobes, pons, medulla and spinal cord

Microscopic examination showed a demyelination of the subcortical white fibers as originally described by Schilder This was accompanied by secondary degeneration of the axis cylinders About the edge of the demyelinated areas, the reaction was most marked, with the broken down myelin taken up as amorphous lipoids by various phagocytic cells, especially the compound granular cells developed from the microglia The oligodendroglia showed edema and general cytolysis The microglia showed extensive hyperplasia, many of the cells forming giant cells

The picture, as a whole, may be summed up as a severe, relatively localized, toxic degenerative process of the brain which ended, theoretically at least, in a diffuse gliosis In addition to these observations, there was a picture of diffuse perivascular hemorrhage strongly suggesting hemorrhagic encephalitis, such as one sees both in the epidemic form and in influenza

DISCUSSION

HARRISON S MARTLAND Was the hemorrhagic feature in this case a late lesion or did it occur earlier in the disease?

L W SMITH I am inclined to think that there was a hemorrhagic factor earlier in the course of the disease, as evidenced by the tremendous hemosiderin reaction practically everywhere in the sections, whereas the acute hemorrhagic picture was merely terminal

HARRISON S MARTLAND Were the hemorrhages ringlike in character, i e were they confined chiefly to the so-called Virchow-Robin space?

L W SMITH Yes, but many of them were much more extensive

HARRISON S MARTLAND It makes me think of the pictures seen in that type of traumatic cerebral hemorrhage characterized by multiple punctate hemorrhages in the deeper portions of the brain i e, the so-called concussion hemorrhages. In the late stages of punch drunk we have described lesions somewhat similar, due to a replacement gliosis in the areas of former hemorrhage. We called attention to the difficulty in the late stages, of distinguishing these traumatic injuries from the lesions seen in paralysis agitans, disseminated sclerosis, progressive lenticular degeneration, chronic epidemic encephalitis and some of the so-called hemorrhagic forms of influenzal encephalitis

CHARLES DAVISON Was there any round cell infiltration and what was the state of the axis cylinders?

L W SMITH The condition of the axis cylinders roughly corresponded to the original descriptions. Centrally they had disappeared, but in the periphery one still could find vestiges of them. There were places of definite perivascular round cell infiltration

HARRISON S MARTLAND The same picture is also seen in hemorrhagic encephalitis following the administration of arsphenamine. Were these lesions chiefly in the cortex of the brain or in the deeper portions?

L W SMITH They were subcortical, the cortex itself practically escaped. There was a sharp line of demarcation between the actual cortex and these lesions, but they extended down as far as the fourth ventricle and the pons to a limited extent

During the last seventeen years there have been fifty-three cases of so-called Schilder's disease reported under various names—some as Schilder's disease, some by the anatomic name, encephalitis periaxialis diffusa—the four cases by Globus and Strauss a year or two ago under the term progressive degenerative subcortical encephalopathy, and others by comparable terms. The chief aim was to differentiate between those which are definitely inflammatory or infectious in nature and those which are of a toxic degenerative character. This case frankly puzzles us as to the group in which it should be catalogued, because clinically it presents the features of an inflammatory disease, while histologically the picture is almost entirely that of a degenerative one, except for this acute hemorrhagic process, so that I do not know whether Schilder's disease is an absolute clinical or even a pathologic entity. Most of the cases have been reported in comparatively young persons. The duration has been from four days to eleven years. One man aged 65 who had had a history of progressive cerebral lesions over a considerable number of years, presented evidence of diffuse sclerosis of the brain. The relationship of the cerebral lesions to the cord lesions—multiple sclerosis and lateral sclerosis—is however extremely problematical, and I do not feel that any of us at the present time are in a position where we can make a definite statement as to the absolute entity of this condition, but it does present certain anatomic features which are relatively constant

ANOMALOUS RAMIFICATIONS OF THE CORONARY ARTERIES WILLIAM ANTOPOL AND M A KUGEL

Three hearts were shown in which the left anterior descending coronary artery arose independently from the left anterior sinus of Valsalva. The artery lying in the bed of the left circumflex coronary artery apparently arose from an independent opening in the right anterior sinus of Valsalva immediately posterior to

the mouth of the right coronary artery. This vessel first pursued a course similar to that of the anastomotic artery type II of Kugel, and then continued at the left border of the heart as the left circumflex coronary artery.

Reasons are given which make it seem probable that this anomalous origin of the left circumflex artery is due to a developmental absence of the first portion of the left circumflex coronary artery, with a resultant widening of anastomotic artery type II which takes over its function.

One of the cases showed atherosclerotic narrowings and closures of the right coronary artery and the left anterior descending coronary artery. The nutrition of the heart was good for some time, however, because of the patency of the first portion of the left anterior descending coronary artery and the entire anomalous vessel.

DISCUSSION

M. A. KUGEL. There are two other factors which may play a part in maintaining the circulation in the heart with multiple closures of the coronary arteries. First, according to Wearn, the thebesian system can take over the circulation when the mouths of the coronary arteries are gradually closed. He has reported two interesting cases in which there was complete closure of the mouths of both coronary arteries due to syphilis of the aorta in these regions. Apparently, in these instances the nutrition of the heart was maintained by the thebesian system.

Secondly, we found that some of the occluded vessels were recanalized and thus also probably aided in maintaining the coronary blood flow.

There are many cases reported in the literature of single coronary arteries, one of which was described by Dr. Plaut.

It is conceivable that the absence of one coronary artery either due to congenital or postnatal closure of the other coronary artery may become clinically significant in that sudden closure of the remaining coronary artery (at its mouth) would probably result in immediate death. In our cases, in which there was an accessory coronary artery, one can imagine that in the event of closure of one or even two coronary arteries, the accessory vessel through its anastomoses would be able to maintain the coronary circulation if the person survived his attack of thrombosis of the coronary arteries.

EMANUEL LIBMAN. In regard to the canalizing vessels, we used to think of them as important in case of coronary thrombosis, but Dr. Bachr several years ago found that the canalized vessels were apt to undergo sclerosis again, and that they did not play as large a rôle in the nourishment of the heart as was believed.

When it comes to the question of death in these cases, there are several questions involved: the suddenness and the completeness of the closure, the size of the vessel involved, the suddenness of the atherosclerosis in the other arteries of the heart, and the presence of such vessels as have been described here.

LOUIS GROSS. I should like to point out one or two anatomic facts in connection with this vessel, which may be of some interest. You will recall that the right coronary artery arises from this point of the aorta (illustrated) and that from it in turn there arises the anastomotic artery type II which Dr. Kugel described in detail. In the anomalies that were shown, the anastomotic vessel arose from the sinus of Valsalva instead of from the main vessel. It must be realized, however, that there are all sorts of variations as to the site of origin of a branch. It can arise directly from a main coronary vessel or it may arise independently from the aorta. I bring out this point in order to show that if the vessel arises from the sinus of Valsalva and not from the main vessel, it does not necessarily militate against its acceptance as a branch from the right coronary artery.

There is another interesting point with regard to these three cases to which I should like to call your attention. It may be a matter of speculation, but we have here some suggestion of an experiment that nature has made for us. The two normal hearts which Dr. Antopol presented showing this anomalous vessel were in patients aged 64 and 67 years respectively. The left descending vessel in both these cases was remarkably free from arteriosclerosis, even at the site of

predilection for this condition. In the third case there was arteriosclerosis of the right coronary artery. It is obvious that an independent origin of the left coronary artery shunts much of the blood away from the opening of the anterior descendens. The question that arises is whether this fact is responsible for the absence of arteriosclerosis at this customary site in the left descendens. I suggest this as it seems interesting that all three cases should lack the lesion so frequently found.

ALFRED PIAUT. I should like to continue in the direction in which Dr Libman has begun. Are we going to be able by continued study of coronary anastomoses to explain the fact that one patient dies suddenly and another patient dies more slowly, and still another survives his coronary lesion for a long time? I am rather skeptical about it. Autopsy revealed a heart with narrowing of the coronary arteries, the wall of the artery was entirely stiff, certainly unable to be closed by spasm. Nevertheless this patient had a sudden attack of angina pectoris and suddenly died. There is a report by Oestreich in which autopsy disclosed a complete old thrombosis of one coronary artery and an obturating embolus in the other coronary artery. We should have expected this man to drop dead. He did not. He lived half an hour after his first sign of cardiac distress. Chiari reported a similar case with death fifteen minutes after the beginning of the attack. Many years ago, Krehl spoke about the X-factor which is interposed between coronary lesion and sudden death. We certainly do not always see a correlation between the extent of the coronary lesion and the suddenness of death. Dr Kugel just said, that a good many cases of absence of one coronary artery are reported in the literature. There are a good number of cases described under this heading, but I do not think there is any one in which there is really absence of the artery. When I published my paper nine years ago, I was careful to simply label it "Blood supply of heart from a single coronary artery." The right coronary artery in our specimen seemed to be missing, but I found a small round dot in the sinus of Valsalva which probably was a rudiment of the artery. Most of the other cases reported are nothing but anastomotic branches from the other coronary artery. Eighty years ago this was plainly stated by Hyrtl.

The comparative anatomy of the coronary arteries is interesting. Two coronary arteries develop, with separation of the heart chambers, in fishes and amphibia. There is only one coronary artery, and in *Chelonidae* and *Sauridae* there is some variation in the number. For nearly a hundred years Kamper's alleged statement that the elephant has only one coronary artery has been quoted. I had an opportunity of seeing the heart of an elephant, and there were two coronary arteries. I went back to Kamper's original description of the elephant's heart. It simply stated that the heart had only one coronary artery, but this divided into two branches directly after the origin of the aorta.

HARRISON S. MARTLAND. In syphilitic aortitis in which there has been a slow atresia or stenosis of the orifices of the coronary arteries, what in your experience has been the condition of the heart muscle? Do you not often find just a nutritive disturbance without extensive scarring?

WILLIAM A. ANTROPOL. We have one case similar to that with almost complete occlusion at the mouth of the right coronary artery. In this case there was dilatation of the anastomotica type II, which joined the left with the right circumflex. It seems as though the right side of the heart was supplied by blood from the left coronary artery by means of the anastomotica. There was no extensive scarring.

HARRISON S. MARTLAND. It would seem that these anomalies must be fairly common. Clinically they are of great importance in the establishment of compensatory circulation in occlusion or atresia of the coronary arteries. Unfortunately it is quite impossible for most of us to study these hearts properly on account of the great amount of time and the difficult technic required.

WILLIAM A. ANTROPOL. The time factor is important. If there is a sudden occlusion and there is no time for anastomosis to develop, it is quite obvious that

there will be no dilatation, but if it is a slow process, like syphilitic aortitis, communicating channels will develop

CHARLES NORRIS I have seen a great many hearts, but never one with a single coronary artery I think the report that only one coronary artery exists is due to careless observation The observers have probably overlooked the fact that there has been a closure of the orifice, and that sometimes one must look very carefully I have seen a number of cases in which there was apparently but one orifice, but dissection always revealed the coronary artery, which was of normal width, 10 or 11 mm in circumference, the circulation had reestablished itself in the coronary the orifice of which was closed I think it a false observation that anyone has seen in the human heart only one coronary artery

ALFRED PLAUT I think I can defend myself by showing Dr Norris a drawing that I brought, by which we can prove that the one existing artery is sending branches to the whole heart, then I think Dr Norris's objection will be withdrawn This coronary artery goes around the whole heart and nearly reaches the point where the other coronary artery should arise It means that the whole heart belongs to the system of this one coronary artery If there had been another coronary artery, one could not explain this system which goes around the whole heart It fulfils the condition which Hyrtl imposed eighty years ago for the claim that a heart has one coronary artery

LOUIS GROSS This should not necessarily fulfil all the conditions In this diagram, if this left anterior descendens arose further along the course of the left circumflex and it may very well do so, and if the circumflex orifice were obliterated, for instance through syphilis, so that all the blood to the left hemisphere came through the anastomotic vessel, much as it is going to the left circumflex in the cases presented here, there would seemingly be a single coronary artery supplying the whole heart The little brown dots referred to by Dr Plaut are interesting, in one case we found tiny dots which indicated that the original site of the blood supply from the left side had come from the left anterior sinus of Valsalva I agree with Dr Norris that the blood supply originating from a single coronary artery must be a rare condition

ALFRED PLAUT In the case I showed, only one vessel comes out from the sinus of Valsalva There is no branching near the origin Here (lantern slide demonstration) is the posterior view of one coronary artery going around the whole heart We see it emerge from one edge and disappear on the other, these are branches coming out, and probably there is an anastomosis which I could not prove by dissection with scissors and forceps Here is the anterior picture This is the left coronary artery, which disappears on the left edge and goes around, and then reappears on the right edge This is the ramus descendens which goes down to the apex of the heart But the branch which it gives off to the right is wider than the one which goes down to the apex In a picture which Henle gives in his "Textbook of Anatomy," he also makes this branch wider

Why do we know so little, practically nothing, about the embryology of the coronary artery? I remember that ten years ago I could not find anything on its origin Why is it that with the extensive literature on the malformations of the heart so little is known about the malformations of the coronary artery? Rokitsansky hardly mentions them in his monograph

EMANUEL LIBMAN I should like to draw attention first to the fact that it is a good thing to look at the pulmonary arteries when studying the coronary arteries, because from time to time an important branch comes from one of the two pulmonary arteries In the second place, there is a little historical interest to this question of the stenoses of the origin of the arteries Many years ago I spoke to Sir Humphrey Rolleston about this subject, and he drew my attention to an interesting book by Dickinson in which one of the papers dealt with narrowing of the orifices of the coronary arteries He described three cases, and among them was the one of Thomas Arnold, Master of Rugby, in whose heart there was supposed to be but one coronary artery Dickinson took that heart out and

he found there was a second artery with closed orifice. It would be interesting to take a series of hearts in which there is a closure from syphilis and find out how often this type of closure is present, and how often such a vessel as that described by Dr Antopol and Dr Kugel is dilated.

The whole subject of the pathogenesis in the clinical picture has never been properly studied, because each man has his own theory. I shall attempt to point out in the next few months that practically every theory that has been suggested in the pathogenesis of angina pectoris is correct, except one, and that is the theory that it is spasm of the heart muscle itself. These theories, however, hold for different cases, and sometimes two theories hold for one case. Therefore it is not possible to talk about death in coronary disease on just one basis. As regards spasm, Dr Plaut mentioned cases in which spasm is presumed to occur and in which there is disease of the coronary arteries. From the clinical standpoint it is easy to presuppose this. That spasm can play an important rôle in so-called angina pectoris is shown by the fact that there are cases on record of patients with Raynaud's disease who died with angina pectoris and with no lesions whatever. I use the term so-called angina pectoris to cover all the types which we see, I refer to the whole group when I say "so-called." There is one case on record in which the patient had Raynaud's disease of the feet and also of the hands for a long time. The patient developed temporary amaurosis, and the vessels in the eyegrounds were found to be narrowed. That patient had a violent attack of angina pectoris and died, there was no disease of the vessels. I think that if spasm itself can cause death, and that if spasm can cause angina pectoris, we have the clinical evidence to show that it may play a rôle even in cases in which the vessels are diseased. We have the same problem in Raynaud's disease. Everybody who has worked on the problem of thrombo-angitis obliterans has drawn attention to the symptoms which may occur from spasm. While I think it is difficult to conceive that spasm may occur in these vessels, I think the question should be left open. In the studies which I have made on the hyposensitive state, I have found that general weakness can take the place of local pain in a given disease in which the main symptom is usually local pain. It is possible for a patient at the onset of spondylitis to drop on the floor in shock, and then get up and begin walking. We must begin to study these cases from the standpoint of the hyposensitive condition. I believe that it is possible, especially in a fatal case, for the patient to go into fatal shock. I want to indicate how difficult it is at the present time to discuss clearly all the possible causes of death.

M A KUGEL. We presented these vessels only to demonstrate their embryologic, anatomic and possible clinical significance.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Jan 13, 1930

HENRY C SWEANY, *President, in the Chair*

THYROTOXICOSIS PERSISTING AFTER THYROIDECTOMY DALLAS B PHEMISTER
and P ARTHUR DELANEY

L B., an unmarried woman, aged 41, was seen by Dr D P Abbott in February, 1925, because of nervousness, weakness and palpitation of the heart. She had a fine tremor and tachycardia, there was no exophthalmos, and the thyroid gland was not palpably enlarged. On February 27, the basal metabolic rate was +12. Rest in bed and the use of compound solution of iodine for two months made no improvement. On July 22, her basal metabolic rate was +89. Rest and the use of compound solution of iodine again had no effect. On August 20, the basal rate was +60, and two days later both upper poles of the thyroid were ligated. She did not improve appreciably from the operation, and the

weakness, tachycardia and nervousness persisted. On Jan 13, 1926, a subtotal thyroidectomy was performed. The thyroid gland was found about normal in size and a small amount of the posterior portion of each lower pole was left behind. The patient improved but slightly after the operation, and two months later she was extremely toxic. On April 20, the basal metabolic rate was +83. The use of compound solution of iodine for several weeks caused no improvement. At this time a thorough examination was made for accessory thyroid tissue and none was found. The patient then received roentgen therapy from May to October, over the neck and mediastinum. There was no improvement in her condition, and during the autumn of 1926 she was confined to bed for two months with symptoms and signs of cardiac incompetency, there was marked edema of the feet and legs, tachycardia and dyspnea. In January and February, 1927, she was again given iodine and on April 20, her basal metabolic rate was +41, but she was still confined to bed with signs of cardiac incompetency. In the belief that too much thyroid tissue had been left behind at the first operation, the neck was explored on June 6. An examination was made from the level of the thyroid cartilage to the thoracic aperture and no tissue like thyroid gland was found. There were two small fibrous nodules in the region of the posterior portion of the lower poles. In an endeavor to do something the remnants of the inferior thyroid artery on either side were ligated. Following this operation the patient improved materially for a short time and on June 14, the basal metabolic rate was +5. Two months after this last operation, however, she was again markedly thyrotoxic and remained so from that time until death. On November 5, the basal metabolic rate was +57, and on Feb 8, 1928, it was +78. She was confined to bed from time to time during the spring and summer of 1928. From June 16 to August 27, the patient received 10 minims (0.6 cc) of compound solution of iodine three times a day. She did not improve and had a basal rate of +78. She entered the Billings Hospital on November 6, with a basal metabolic rate of +85. There had been no appreciable change in her condition. She received extract of suprarenal cortex for two months without effect. On Jan 10, 1929, her basal metabolism was +69, and she had marked weakness and signs of a moderate cardiac decompensation. While she was under observation, several blood calcium determinations were made that gave normal results. Information secured from her parents added that about the middle of January, she had a severe attack of acute pain in the region of the right kidney accompanied by chills, a temperature of 103 F and bloody urine. Early in February a urinalysis was done that was reported albumin 2+, leukocytes 1+ and erythrocytes 3+, on the same date, her leukocyte count was 18,000, erythrocytes 2,800,000 and hemoglobin 50 per cent, while the differential count revealed 90 per cent neutrophils. It is interesting to note that previous to this acute attack the leukocyte counts had been under 10,000, and in the differential examination there was an increase in the lymphocytes up to 62 per cent. The patient died on February 16.

On February 17, autopsy was performed and disclosed, among observations of lesser interest, a slight acute vegetative, mitral endocarditis, hemorrhagic glomerulonephritis and anemic infarcts in the right kidney and spleen. The thymus gland weighed 6 Gm. From the neck, tissues, including and below the thyro-cricoid cartilage, were removed and carefully searched for thyroid tissue. Many microscopic sections failed to disclose a solitary thyroid follicle. Material that grossly suggested thyroid tissue, microscopically proved to be a lymph node.

In view of these results following such a persistent thyrotoxicosis, interest was stimulated in making a special histologic study of the thyroid removed as a subtotal resection in January, 1926. Sections were prepared from different levels of four pieces of tissue secured from the Bevan Laboratory of the Presbyterian Hospital, Chicago. The use of a number of different staining methods has enabled us to demonstrate the following conditions. The presence of characteristic lymphoid follicles with germinal centers, with associated lymphoid tissue frequently arranged in the cortex and medulla, and thyroid alveoli free among

the lymphoid tissues, extensive arteriosclerosis with calcification of the thyroid arteries, and of their branches, extensive fibrosis and masses of granulation tissue, two distinctly different types of thyroid alveoli, morphologically and cytologically, (a) alveoli of moderate size lined by low cuboidal cells with relatively clear cytoplasm and an average content of vesicular colloid in the lumen, (b) smaller alveoli resembling those of compound, serous, alveolar glands, with very small lumen that are often empty, or else contain very little colloid, and lining cells that are tall cuboidal to columnar with a generous quantity of deeply staining granules of mitochondrial type, occasionally seen as isolated or grouped units in the wall of the alveoli described under (a)

DISCUSSION

EMIL RIES Were the ovaries examined?

EDWIN F. HIRSCH How do the authors explain their results?

GEORGE M. CURTIS The case which Dr. Delaney has presented raises a number of interesting questions regarding the problem of goiter. It seems open to question in this case whether a complete removal of the thyroid was done. The main portion of the thyroid gland originates at the base of the embryonic tongue in the region of the foramen cecum. This anlage may not descend into the neck. In case it does not, it persists as a lingual thyroid and this may become goitrous. More than 100 cases of lingual goiter have been reported in the literature. At least one of these (Strauss, *Med. Klin.* 2:1259, 1906) was associated with mild symptoms of thyrotoxicosis.

The collections of lymphocytes within the thyroid gland, and particularly their organization into a definite lymph nodule, as has been shown, recalls that patients with thyrotoxicosis have, as a rule, lymphocytosis. This may be as high as 65 per cent. A lymphocytosis, however, is not pathognomonic of thyrotoxicosis since it also occurs in endemic cretins. Just what its significance is in thyroid disease is by no means clear.

Calcification of the thyroid arteries in goiter has been well recognized, particularly by Langhans and his school. Jores (*Beitr. z. path. Anat. u. z. allg. Path.* 21:211, 1897) demonstrated early changes in the walls of goitrous thyroid arteries leading to arteriosclerosis. These consist of widening of the intima, fragmentation of the internal elastic membrane and finely granular calcification in and about the fragments. Hesselberg (*Frankfurt Ztschr. f. Path.* 5:322, 1910) observed sclerotic plaques in the thyroid arteries of the new-born infant. Isenschmid (*Frankfurt Ztschr. f. Path.* 5:205, 1910) reported arteriosclerosis in the thyroid arteries of infants. Arterial changes may occur early in the walls of the thyroid arteries without a generalized arteriosclerosis, and particularly in endemic goiters. The reasons for these early degenerative changes are not clear.

FRANK SMITHIES In a given individual or group the amount of thyroid tissue necessary to cause thyrotoxicosis is not known and possibly only a small amount suffices. In a thyroid constitution only a small quantity of thyroid tissue may be necessary to continue the symptoms.

P. A. DELANEY The ovarian tissues were examined without demonstrating important changes. Dr. Phemister and I are at a loss to explain our results.

THE EFFECT ON MOTILITY OF IRRIGATING A LOOP OF ILEUM OF MACACUS RHEUS MONKEYS WITH SALMONELLA ENTERITIDES AND ITS PRODUCTS G. M. DACK and R. MERCHANT

In previous work we had observed that not all monkeys were susceptible to "food poisoning." In the monkeys that were susceptible, however, diarrhea could be produced time after time by subsequent feedings of living *Salmonella* organisms. In the present series, therefore, only such monkeys were used as were known to be susceptible.

Fistulas were made on the ileum of four monkeys, three of the Thiry type and one of the Thiry-Vella type. Motility of the loops was studied by the balloon method.

Irrigation of the loop with heat-killed cultures and filtrates of *S. enteritidis* (550) did not produce any striking changes in motility and tonus.

Observations were made on the stools of one monkey with a Thiry fistula and one with a Thiry-Vella fistula. No diarrhea followed the irrigation of the loops with heat-killed cultures, filtrates or living suspensions of *S. enteritidis*. Living organisms, however, when fed produced a diarrhea in the monkey with the Thiry-Vella fistula, without affecting the loop motility.

Endoplates streaked with the loop contents of the monkey with the Thiry-Vella fistula showed few or no colonies. No *S. enteritidis* organisms were recovered from the loop thirty hours after irrigation with a living suspension of *S. enteritidis*.

INTERMITTENT FECAL ELIMINATION OF BACTERIA IN CHRONIC BILIARY CARRIERS LLOYD ARNOLD and A. J. NEDZEL

There are certain demonstrable changes that take place within the gastrointestinal tract during the process of adaptation to external stimuli, such as alterations in climate and in diet. The bacterial content of the lumen of the upper half of the small intestine is low and consists of enterococci in normal animals, including man. This bacterial flora is not changed by the ingestion of bacteria. These exogenous strains are destroyed within this part of the intestinal tract. The simple and scanty bacterial life within the lumen of the duodenum and jejunum is a constant observation for normal animals.

The bacterial contents of the small intestine can be changed in several ways. We have found that a warm temperature environment will cause a change in the bacteria in the duodenum and jejunum. Accompanying this change in the endogenous bacterial flora there is a loss of the power to destroy ingested bacteria. When bacteria are injected directly into the duodenum of normal animals few of them can be found in the cecum. When the same experiment is performed in a warm temperature room, many of them reach the cecum and remain viable for hours. This shows that the intestinal tract can destroy bacteria independent of the stomach.

B. prodigiosus was injected into the gallbladder of dogs under sterile precautions. Nonleaking appendiceal fistulae were established. After from seven to ten days six animals showed no *B. prodigiosus* in the cecal contents, four animals had a few isolated colonies after direct plating of the contents. When these animals were placed in a warm and humid room for three hours, many *B. prodigiosus* were present in the cecum and persisted for many hours. Agar stab cultures of *B. prodigiosus* were sewed into the lumen of the gallbladder in dogs. This led to a more persistent carrier state and more of these microorganisms could be found in the cecum from one to four weeks after recovery. When these animals were placed in the hot room, many more bacteria appeared than in ordinary temperature rooms. This was a substantiation of our previous experimental work, namely, that interference with the self-disinfecting power of the small intestine would allow patients who have recovered from typhoid fever some time ago to become fecal carriers. The hot weather causes an interference with the bacterial killing power of this region of the intestinal tract. Patients recovered from typhoid fever who show an absence of *B. typhosus* in the feces may have small lesions along the biliary tract that eliminate these bacteria into the duodenum but under normal conditions they are destroyed before reaching the large intestine. If the self-disinfecting power of the small intestine is absent, then such persons would be carriers. The same is true of the water-borne and food-poisoning diarrheas.

In many instances the epidemiology of typhoid fever following a water-borne diarrhea or food-poisoning epidemic has been difficult to explain. No bacteria

resembling the typhoid group can be isolated from water or food in a great many instances. The appearance of typhoid fever in the warm months of the year has been difficult to explain epidemiologically. The ingestion of polluted water causes diarrhea. There is a loss of the self-disinfecting power of the upper part of the small intestine during diarrhea. The same is true of diarrhea due to food poisoning.

DISCUSSION

FRANK SMITHIES. Were the results with tissue-invading organisms such as *B. typhosus* the same as with the lumen-dwelling organisms?

L. L. ARNOLD. We could not work quantitatively with organisms of the typhoid group as well as with the nonpathogenic chromogens used.

BIFID APEX OF THE HEART OF A GUINEA-PIG H. B. HANSON

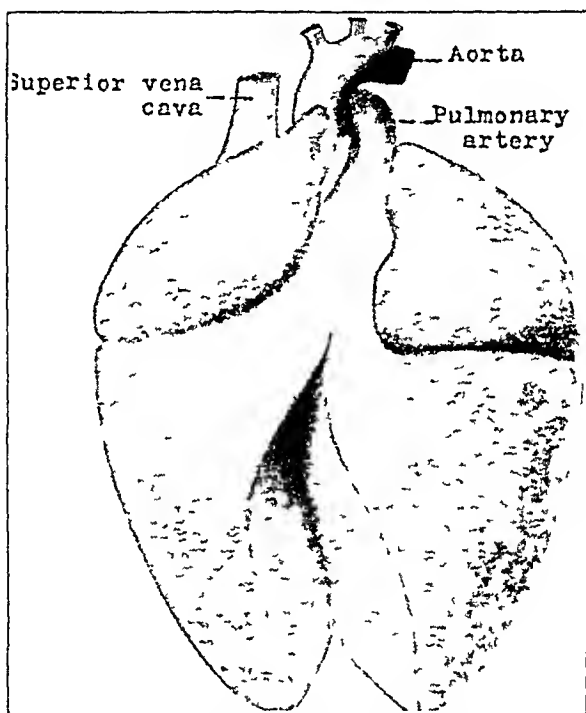
A more or less complete congenital separation of the ventricles of the heart through the septum is known as bifid apex of the heart. Judged by the dearth of recorded accounts it seems to be a rare anomaly. I have found only four references to this anomaly in human hearts published in ninety years. H. D. Rolleston (Bifid Apex of the Heart, Tr. Path. Soc. London **43** 37, 1891-1892) described briefly the heart of a woman, aged 40, who died of stenosis of the mitral and aortic valves. The apex of the heart was formed by the left ventricle, and extending from the right side of this was a second apex that of the right ventricle. A. W. Meyer (Hearts with Bifid Apices, Anat. Rec. **9** 524, 1915) published illustrations of two hearts with deeply notched apices but included no descriptive details. F. P. Mall (Bifid Apex of the Human Heart, Anat. Rec. **6** 167, 1912) recorded a heart with bifid apex found in a cadaver at Johns Hopkins University. The cleft was 2 cm deep and the anomaly was attributed to an arrested development of the apex in an embryo more than 11 mm long. Maude E. Abbott (Congenital Cardiac Disease in Osler, William. Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1928) stated that in her list of 850 congenital cardiac defects, bifid apex occurred fifteen times with and independently of other defects. She also referred to Thoremin's 106 cases in which bifid apex occurred three times.

According to F. P. Mall (On the Muscular Architecture of the Ventricles of the Human Heart, Am. J. Anat. **11** 211, 1911), the superficial muscle fibers of the ventricles are divided into two main groups. One system, the "bulbospiral" band, arises from the conus arteriosus and the root of the aorta. The other, the "sinospiral" band, has its origin from the region of the primitive venous sinus. The fibers of each of these systems normally cover portions of each ventricle. They extend from above obliquely downward and at the apex all are coiled into a whorl or vortex. From this all pass to the interior of the walls and then back to the base of the ventricles, some in the septum and others in the papillary muscles. Mall stated that a bifid apex results when there is a defect in the formation of the normal muscular vortex. This occurs because the sinospiral muscle band does not reach the apex of the left ventricle, and the apex, therefore, is formed by the bulbospiral band and consequently the inter-ventricular groove persists.

According to Mall bifid apex is commonly found in some marine animals such as the dugong, but no reference could be found of its occurrence in any of the higher vertebrates although texts on comparative anatomy, embryology and various species of animals were examined. Dr. W. J. Osgood, curator for the department of zoology at the Field Museum, Chicago, assisted in offering his library and that of the museum for additional study but here also no information was found regarding bifid apex of the heart in the higher vertebrate forms. It is impossible to estimate, therefore, the frequency of occurrence of this anomaly in the higher vertebrates.

During the routine postmortem examination of a guinea-pig in the laboratory of St Luke's Hospital by Miss Marian Barnes, the ventricles of the heart were found to be separated along the interventricular septum. Since an average of 250 guinea-pigs is examined postmortem each year in this laboratory without an anomaly of this kind having been noted, this congenital deformity was considered to be rare. A careful examination of the heart was then made and a search established for reports of a similar anomaly in man and the higher animals.

The heart with its thin, transparent pericardium occupied the usual position in the thorax. After the pericardium had been opened there was a median longitudinal division of the septum and although the ventricles were close together they were separate and each had a complete wall of its own. The septal surfaces of the approximated ventricles were smooth and glistening and had no hemorrhages such as occur in freshly divided tissues and which would have been present had the septum of the heart been accidentally divided by the scissors.



Ventral view of the heart, illustrating the extent of bifurcation of the apex

used in opening the pericardial sac. The approximated surfaces did not lie in a straight sagittal plane, but instead the septal wall of the right ventricle was a concave surface that cupped itself over the convex septal surface of the left ventricle like the approximated paired kernels of a double almond. The heart was then removed with the stumps of the large vessels intact. The anterior length of the left side of the heart from the root of the aorta to the apex was 2 cm and the right, 1.9 cm. The fissure mentioned extended on the anterior surface from the apex upward 1.2 cm to the lower margin of the left auricular appendage and on the posterior surface upward 0.7 cm. The apex was thus completely divided for a length of 7 mm. The dorsoventral diameter of the heart at the upper level of the fissure ventrally was 1.1 cm and the dorsoventral extent of the fissure at the same level was 1 cm. The remainder of the ventricles above the completely divided apex were therefore connected only by a band of myocardium about 1 mm in thickness on the posterior surface of the heart. There was no connection below between the ventricles. The large vessels at the base of the heart had the usual relations. The ductus Botalli was closed but a fibrous cord persisted 0.4 cm long and 0.1 cm in diameter.

The inside length of the left ventricle from the mitral ring to the apex was 11 cm and from the attachment of the aortic leaflets to the apex it was 13 cm. The thickness of the myocardium of the left ventricle measured along the septum behind at the level of the mitral ring was 3 mm. The length of the right ventricle from the tricuspid ring to the apex was 11 cm and from the attachment of the pulmonic leaflets to the apex it was 14 cm. The thickness of the myocardium of the right ventricle measured along the septum in front was 1 mm. The diameter of the tricuspid ring was 7 mm, of the pulmonic 2 mm, of the mitral 6 mm and of the aortic 2 mm. There were no abnormalities of the leaflets of any of the valves.

The heart described in this report was unusual in that the ventricles were separated at the auriculoventricular junction.

Book Reviews

MOLECULAR PHYSICS IN RELATION TO BIOLOGY Report of the Subcommittee on Molecular Physics, of the National Research Council Price, \$3 Pp 293, with 71 line-cuts and 2 plates Washington, D C National Research Council, 1929

The National Research Council has performed a useful service in publishing this compilation of contributions which serve notice that molecular physics is hereby recognized as one of the official routes for invasion of the problems of biology As du Nouy says in his stimulating introductory chapter, "Molecular physics deals mainly with the physical properties of molecular arrangements The name itself is relatively young, but the techniques employed are those of physics, of physical chemistry, and of chemistry, and for that reason, it may be said that most biologic problems depend on molecular physics for their solution An isolated phenomenon may be of chemical nature, yet its consequences, in the organism as a whole, may be purely physical" Actually, molecular physics covers the same ground more familiarly designated by the term colloidal chemistry, and the theme of this volume is largely a reiteration of the well known fact that biologic phenomena are not all due to reactions between chemical valences, but also to physical interaction between large molecules Du Nouy stresses as the main objective the enlisting of the interest and cooperation of physicists in the problem of biology by placing before them these problems, not as isolated mysterious units, but as expressions of the same fundamental principles and laws which govern the inanimate world, and to direct their attention to the existence of this bridge, "directly connecting physics and chemistry over the chasm of chemical methods"

The several authors each present brief statements of their own particular fields of interest, starting out with Ascoli's description of his mostagnum reaction which he brought out in 1909 as a new method for investigation of immunologic reactions by observing the change in surface tension accompanying them He admits that the general neglect of this method by immunologists is justified by its inferiority to other methods as a practical diagnostic procedure, but presents claims as to its possible value in the diagnosis of cancer This paper seems out of place among the following much more definite articles, which deal mostly with exact and comprehensive observations Thus, Chambers describes the work that has been done, largely by himself, in estimating the hydrogen ion concentration and the oxidation-reduction potential of cytoplasm by micro injection methods Donnan reviews in three pages the investigations that have been made on the Donnan equilibrium, and points out that the general thermodynamical equation which is applicable to the case of ionic membrane equilibria has been lying buried all these years in Willard Gibbs' celebrated memoir on heterogeneous equilibrium More extensively are presented the principles, methods and mathematics for investigation of surface tension by N E Dorsey, and the mechanism of filtration through porous membranes by Leonor Michaelis Osterhout reviews and summarizes his important work in the permeability of cells, and du Nouy does the same for his pioneering attempts at a study of the physical chemistry of immune serums Northrop presents a brief statement on the nature of viscosity and its measurement, while Seifriz gives a much more detailed report on the viscosity or plasticity of protoplasm as determined by himself and other investigators Vles and de Coulon offer a resume of their attempts to influence the growth of tumors by modifying the iso-electric point of the tissues Each article is accompanied by a useful bibliography It will be seen that these papers are a somewhat heterogeneous lot which present a few isolated, often unrelated topics of interest to the general biologist as well as to the "colloid chemist" Presumably the committee that put out this compilation was largely actuated by thoughts of the careers of the little acorns

THE CHEMICAL ASPECTS OF IMMUNITY By H GIDEON WELLS Second (revised and enlarged) edition American Chemical Society Monograph Series Price, \$6 Pp 286 New York The Chemical Catalog Company, Inc, 1929

Immune reactions, irrespective of whether the mechanism involved is colloidal or what one may call strictly chemical in nature, are fundamentally chemical reactions and their study therefore properly belongs to the field of biologic chemistry. The first edition of this book, which appeared about four years ago, was, however, the only one, at least in the English language, which emphasized the chemical aspects of immunology. Although the general plan and purpose of the book remain unchanged, a great deal of material has appeared during the last few years which bears on this subject and which has been incorporated into the new edition. Among the outstanding items discussed in the present revision are "the newer contributions on the influence of lipoids and carbohydrates on antigenic activity and specificity, the refining of antibodies to near the vanishing point, the chemical modification of antigens, the increasing study of isolated antigens, the growing recognition of the differences between complex and simple antigens, and the varied if unsuccessful attacks on the problems of specificity." The author presents a vivid picture of the present state of the relationship between immunology and chemistry which should prove a thrilling adventure to the workers in both sciences, and especially in chemistry, who are not familiar with the important bond between them and the benefits to be derived from each.

The science of immunology, originally concerned with disease, has developed so rapidly in the last quarter of a century that we may well consider it as a border science between biologic and colloid chemistry on the one hand and bacteriology and the other medical sciences on the other, in much the same way that physical chemistry is considered a border science between physics and chemistry. The advances in immunology have been almost entirely empiric, as in any new science, but we are gradually approaching the time when immune reactions may be placed on a sound theoretical foundation. For this purpose, however, we must develop workers who are familiar with the fundamental ideas and methods of both parent sciences. Some of the most important and perplexing problems in biochemistry, such as the structure of the protein molecule, are indissolubly bound up with such problems as the chemical nature and specific reactions of antigens, and any advances in one field are bound to be reflected in the other. Relationships of this sort may be cited in great numbers, and it is because the present volume reviews the progress made thus far in this highly important border science and because it emphasizes the contributions which biochemistry and immunology are capable of making to each other that it forms a stimulating addition to both the chemical and the immunologic literature.

THE RIGHT HONOURABLE SIR THOMAS CLIFFORD ALLBUTT, KCB, MA, MD, FRCP, FRS, HON MD, DSc, DCL, LL D, Regius Professor of Physic in the University of Cambridge. A Memoir By Sir Humphry Davy Rolleston, GCV O, KCB, MA, Regius Professor of Physic in the University of Cambridge. Cloth Price, \$6 Pp 314, with 3 illustrations. New York The Macmillan Company, 1929

Clifford Allbutt lived for eighty-nine years. His active medical life, which continued until his death in 1925, covered sixty-five years. He made many additions to medical knowledge and technic and he was for many years one of the most influential, widely respected and honored English-speaking physicians. He invented the form of clinical thermometer now in use, he described syphilis of the cerebral arteries in 1868, before Heubner, he exploited the value of the ophthalmoscope in general medicine, he urged the study of pathology on a comparative basis, he advocated the aortic origin of angina pectoris and separated hyperpiesia (essential hypertension) from other forms of increased blood pressure—to mention only some of his achievements. He maintained consistently throughout his long life a wonderful energy and an unceasing work. "Only two things

are essential—to live uprightly and to be wisely industrious” He was a profound student of the history of medicine, a master of literary style and a scholar in the large sense He was in rare degree versatile, learned, wise and kind, and his influence went far and deep The life by his successor as regius professor of physic at Cambridge is concise and compact It traces his multifarious activities succinctly year by year without losing touch with the man himself, and gives a clear and well defined picture of the life of a great personality

DISEASES TRANSMITTED FROM ANIMALS TO MAN By THOMAS G HULL, Chief Bacteriologist, Illinois Department of Public Health, Assistant Professor of Pathology and Bacteriology, University of Illinois College of Medicine With an Introduction by Veranus A Moore, Director, New York State Veterinary College, Cornell University Price, \$5 50 Pp 352, with 29 illustrations and 43 tables Springfield, Ill Charles C Thomas, 1930

In the broad field of comparative pathology there is no subdivision of greater concern to human and to veterinary medicine than the one considered in this book, transmissible diseases common to animals and man

There are five sections Section one deals with diseases of domestic animals and birds that may be transmitted to man tuberculosis, anthrax, foot-and-mouth disease, infectious abortion (‘Brucellosis’ would be a good general term for the animal and human infections caused by the *Brucella* group), milk sickness, actinomycosis, smallpox and cowpox, glanders, rabies, psittacosis, food poisoning, swine erysipelas and parasitic diseases, including the broad fish tapeworm In section two, rodent diseases are considered plague, tularemia, spirochetal jaundice, ratbite fever and Rocky Mountain spotted fever The third section is devoted to the relation of certain human infections to animals, e g, epidemic sore throat, diphtheria and scarlet fever, but diseases like malaria, yellow fever, typhus fever and trench fever, which are conveyed from man to man by insects, are not discussed Section four deals with animals as passive carriers of pathogenic germs, as illustrated in botulism, tetanus and gas gangrene In the fifth section is a brief review of the part played by each animal in the spread of human diseases

There is an author as well as a subject index If a new edition is published, special care should be used to secure the correct spelling of proper names This will be a good book to consult mainly for bald facts in respect to the epidemiology and prevention of the diseases that fall within its scope The historical development of the knowledge of these diseases is given rather full and suggestive consideration

THE EFFECTS OF HIGH VOLTAGE CATHODE RAYS ON THE GERMINAL EPITHELIUM OF THE RAT^{*}

VICTOR C JACOBSEN, M D

ALBANY, N Y

The biologic action of cathode rays has been studied in various laboratories since Coolidge, in 1926, devised a tube which made it possible to observe the effects of the cathode rays outside the apparatus at extremely high voltages. For several years previously, however, Pauli and his co-workers had been making fundamental contributions on cellular alterations in plants, bacteria and wounds, and in the skin of cold-blooded and warm-blooded animals. The extent of their work was limited somewhat by the low maximal voltage which their modified Lenard tube could withstand.

Some practical applications of cathode rays have also been made by Baensch and Finsterbusch¹ in Leipzig who reported success in the treatment for lupus, tuberculosis, verrucosa cutis, psoriasis, infected superficial wounds and cancrs. They used 95 kilovolts, 3 milliamperes, at 5 cm distance for from fifteen seconds to two minutes. They urged caution in the use of cathode rays because of the lack of knowledge of the biologic effects on the operator and patient.

Guyer and Daniels² studied the effects of cathode rays on experimental cancers in rats. They found that with tumors not too far advanced the first irradiations had a detrimental effect, but that successive irradiations probably stimulated the tumor. They estimated the maximal penetration of the effective rays into living cancers as 0.5 cm. *Drosophila* eggs were killed in five-tenths second or less. The lethal period of exposure for a normal rat irradiated over the belly was from three to four minutes. There was no tendency toward formation of

^{*} Submitted for publication, Dec 16, 1929.

^{*} From the department of pathology of Albany Medical College.

^{*} This work was aided by a grant from the Committee on Scientific Research of the American Medical Association.

1 Baensch, W, and Finsterbusch, R. Unsere klinischen Erfahrungen mit der therapeutischen Anwendung von Kathodenstrahlen, München med Wchnschr **51** 2171, 1927, Weitere klinische Beobachtungen bei der Behandlung mit Kathodenstrahlen, Klin Wchnschr **15** 681, 1928.

2 Guyer, M F, and Daniels, F. Cancer Irradiation with Cathode Rays J Cancer Research **12** 166, 1928.

cancer in the rat's skin The action of the cathode rays on tumor was regarded as direct and not systemic

Stenstrom, Watkins, Nurnberger and Fallon,³ also using the Coolidge cathode ray tube, observed the effects of irradiating the rabbit's ear on the leukocytic formula The immediate reaction was an absolute increase in both neutrophils and lymphocytes, the numbers returning to normal in a few hours A sustained reaction of slight absolute increase in neutrophils and a relative and absolute decrease in basophils and monocytes after two days were found

The genesis of roentgen rays occurs when cathode rays impinge on matter, the spectrum varying with the composition of the anodal target These roentgen rays, in turn on striking tissue or some other form of matter give rise to secondary cathode rays The amount of roentgen rays produced by cathode rays of 200,000 volts, using a target as efficient as one composed of tungsten, is relatively minute, hence the roentgen rays generated by cathode rays striking animal soft tissues, which are largely composed of carbon, hydrogen, oxygen and nitrogen, elements of low atomic weight would be of exceedingly smaller amount, although very penetrating Any changes observed in the short distance of the thickness of the rat's skin and underlying organs would in all probability be due to the primary cathode rays, and any differences in effect as seen in the various types of tissue should be explainable on the basis of differences in tissue susceptibility Studies directed at finding proof of this concept, in biology, may seem chiefly of academic value, but the work of Pauli and his group, of Coolidge and his assistants and of Baensch and Finsterbusch indicates that cathode rays have some definite therapeutic applications, although to the present time they have been found, as a whole, inferior to roentgen rays Nevertheless, the making available in this manner of so tremendous an electric potential may lead to discoveries of more pronounced value

In February, 1928, we reported from this laboratory the changes occurring in the abdominal skin of the white rat following exposure to cathode rays⁴ The voltages used were 100,000, 200,000 and 350,000 The current was 1 milliampere The animal was placed 2.5 cm from the anodal window and was entirely protected by copper foil, except for the small area irradiated

It was found that the intensity of the reaction in the skin varied according to the voltage and the length of exposure to the cathode

3 Stenstrom, W., Watkins, C. H., Nurnberger, C. E., and Fallon, M. The Influence of Cathode Rays on Leukocytes of Rabbits, *Proc Soc Exper Biol & Med* **26** 380, 1929

4 Jacobsen, V. C. and Waddell, K. C. The Effects of High-Voltage Cathode Rays on the Skin of the Rat, *Arch Path* **5** 195 (Feb.) 1928

rays Marked gross changes were produced discoloration, depilation congestion, edema, later ulceration and rather sluggish healing of the ulcer

Microscopically, the most characteristic lesion was found to be a fusing of the collagen fibers of the corium and necrosis of the epithelium of the skin and hair follicles. Altered staining properties indicated profound chemical changes with the production of an acid reaction. The vascular injury was not severe and occurred after the hyalinization of the collagen. The depth of penetration of the primary cathode rays as measured by the thickness of the zone of fused collagen varied from 0.07 to 0.22 mm, as seen in the stained section. Allowing for shrinkage of the tissue in the various fixing and dehydrating fluids, one concludes that the penetration was probably about twice that depth.

The peculiar degeneration of the collagen is apparently similar to that caused by exposure to roentgen rays, hence the evidence was regarded as confirmatory of the hypothesis that the biologic effects of roentgen rays are not due primarily to the roentgen rays but to the cathode rays which the roentgen rays produce in the tissues.

One of the goals of research in pathology is to discover in organs, tissues or their component cells alterations which are characteristic or pathognomonic for a given condition. The macroscopic lesions in many diseases are well known and almost as constant as the normal anatomic format. Also, the microscopic picture of cell arrangements and certain finer cell changes can be included in the category of well established anatomic accompaniments of many diseases.

It is quite as essential to identify what are beyond reasonable doubt the characteristic or unique effects of the various forms of light. The lesions caused by roentgen rays in human and lower animal tissues have been repeatedly studied by numerous investigators ever since Roentgen's original discovery. A characteristic single effect is acute hyaline degeneration of collagen fibers, as pointed out by Wolbach⁵ and others. In addition, there are obliterative vascular reactions, hyperplastic epithelial, later atypical epithelial changes and the production of skin cancer.

Chromatin is greatly affected by roentgen rays but not in a manner that permits a diagnosis of roentgen injury solely on the basis of structural alterations in chromatin. It is possible, however, to damage the nucleus profoundly without injuring the cytoplasm. For instance, *in vitro*, heart muscle of an embryonic chicken will continue to beat for days after the nucleus has been killed by exposure to a lethal

5 Wolbach, S. B. A Summary of the Effects of Repeated Roentgen Ray Exposures upon the Human Skin, Antecedent to the Formation of Carcinoma, *Am J Roentgenol* **13** 139, 1925.

dose of radium ⁶ Trypanosomes so exposed may retain their motility, but cannot divide ⁷

Recently, Cramer ⁸ suggested that in death from roentgen irradiation destruction of the organs of the reticulo-endothelial system has taken place. Organs characterized by the capacity to absorb dyes during life are likewise affected directly by irradiation. He saw an analogy between the action of histamine and the intoxication due to roentgen rays in the vagotonia, acidosis and leukocytic formula of the latter condition. The clinical picture of intoxication due to roentgen rays is not clearcut and only adds further stress to the assertion that in the present state of knowledge one knows few absolute criteria for diagnosing a "burn" by the roentgen rays, whether it is in the skin or in a deeper organ.

The male and female germ cells are exquisitely sensitive to roentgen rays. Perthes,⁹ in 1903, was the first to point out the relationship between the activity of reproduction in tissues and the degree of radio-sensitivity. He worked on developing eggs. In 1906, Bergonie and Tribondeau,¹⁰ following work along similar lines, formulated a statement or "law" which is as follows: "Les rayons X agissent avec d'autant plus d'intensité sur les cellules que l'activité reproductrice de ces cellules est plus grande, que leur devenir karyokinetique est plus long, que leur morphologie et leurs fonctions sont moins définitivement fixées." (The x-rays act on the cells with such intensity that the reproductive activity of the cells is greater, their karyokinetic growth is longer and their morphology and functions are less definitely fixed.)

Our previous work on the skin of the white rat ⁴ indicated that at least one supposedly characteristic effect of roentgen rays (acute hyaline degeneration of collagen) could be produced by the direct action of electrons or cathode rays of high velocity. It was therefore believed advisable to study the reactions of the more sensitive germinal epithelium to cathode rays. The testes of the rat are readily available for such an experiment, but since they are covered by skin any changes in them would have to be explained as due to their being more sensitive than the unaffected layer of subcutaneous connective tissue below the level

6 Prime F. The Action of Radium on Embryo Heart Muscle, Proc New York Path Soc **16** 56, 1926

7 Halberstaedter, P. Experimentelle Untersuchungen an Trypanosomen über die biologische Strahlenwirkung, Berl klin Wchnschr **51** 252, 1914

8 Cramer, H. Studien zur biologischen Wirkung der Rontgenstrahlen, Strahlentherapie **28** 431, 1928

9 Perthes. Versuche über den Einfluss der Rontgenstrahlen und Radiumstrahlen auf die Zellteilung, Deutsche med Wchnschr **30** 668, 1904

10 Bergonie, J, and Tribondeau, L. Interpretation de quelques resultats de la radiotherapie et essai de fixation d'une technique rationelle, Compt rend Acad d sc **143** 983, 1906

of the upper 0.2 to 0.4 mm, which was the "zone of effect," as determined by our previous experiments on the rat's skin

TECHNIC OF THE EXPERIMENT

In a previous publication from this laboratory was described a method of exposing a rat in front of the anodal window of the Coolidge cathode ray tube. The experiments to be reported here were performed in the same manner except that the testes were exposed rather than the abdominal skin, that is, the scrotum containing the testes. The animal was tied to a board, the scrotum being 2.5 cm from the anode. The rest of the animal was covered with copper foil. The scrotum was shaved before exposure, because a thin covering of hair is sufficient to stop many of the rays. The shaving was usually done several hours before the experiment in order that any hyperemia due to the friction involved in the shaving process would have time to subside. At first, only one testis was irradiated, the other being used as a control, this method being fairly satisfactory as a whole. Difficulty was encountered, however, at times, in preventing some exposure of the control side because of the spasmodic movements of the animal.

TABLE 1—*Protocol of the Experiments*

Number of Rats	Time of Exposure, Seconds	Voltage
3	0.5	200,000
6	1.0	200,000
8	5.0	200,000
4	10.0	250,000
4	15.0	250,000
3	20.0	250,000
3	30.0	250,000
6	Normal controls	

Also there was histologic evidence in a few rats of a "spreading" effect, that is, cathode ray changes could be detected on the medial side of the control testis where it was close to the exposed testis. Totally unirradiated animals of the same age and condition and from the same pens were regarded as more satisfactory controls. Hence in the later work both testes were irradiated.

The actual irradiation was done in the research laboratory of the General Electric Company in Schenectady, N. Y., with the cooperation of Dr. W. D. Coolidge and the invaluable technical assistance of Mr. C. N. Moore.

Thirty-seven adult white rats were used in this investigation. They were about 5 months old and apparently healthy and virile. The voltages used were 200,000 and 250,000, about equally divided as to number of animals. The current was 1 milliamperes. In no instance was an anesthetic used, nor was the testis ever exposed directly. It was thus possible to study also the cutaneous changes of the scrotum and to compare them with the cutaneous reactions of the abdominal wall as previously reported.

OBSERVATIONS

Immediately after the irradiation, the hairs bordering the shaved zone were seen to have turned a definite yellow. There was also some edema, with vascular dilatation, which became marked in twenty-four hours. The severity of the reaction seemed roughly proportional to the voltage and time of exposure. The irradiation was accomplished in

interrupted exposures of one second each with about one-half second intervals

The superficial epidermis began to desquamate in forty-eight hours, and considerable drying of the skin occurred. Intracutaneous hemorrhage and edema became more marked, but no definite ulcer with moist surface developed. It seems unlikely from gross appearances that infection played any important rôle in the subsequent events.

The animals which were subjected to five-tenths second and one-tenth second exposures had slight local reactions, and after the superficial flaking off of loosened epithelium and a mild edema the skin in

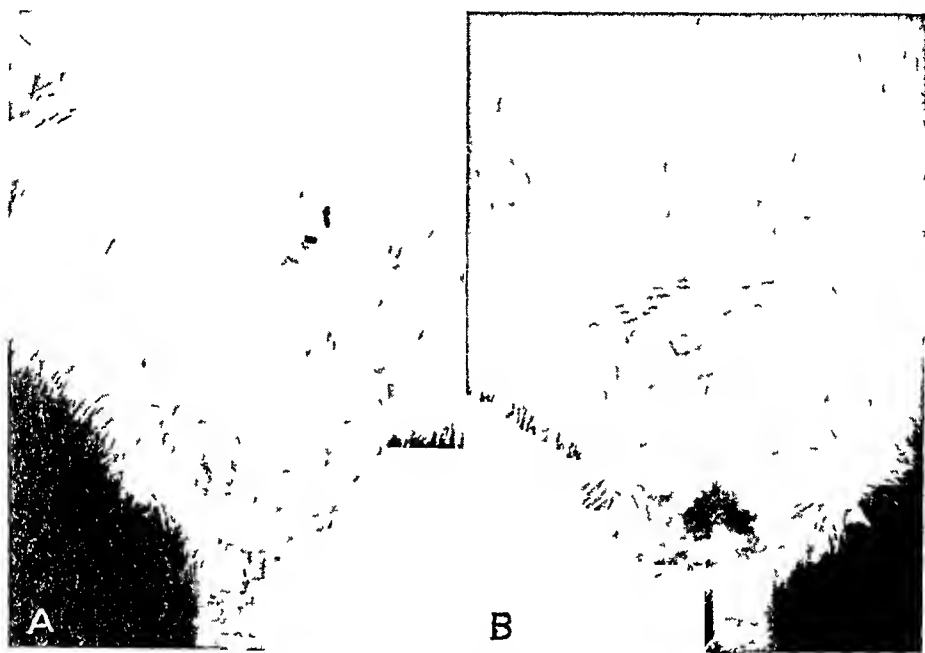


Fig 1—*A*, scrotal area (rat 42) twenty-five hours after irradiation for fifteen seconds at 250,000 volts, showing edema of the scrotum and some discoloration with hemorrhage into the skin

B, scrotal area (rat 43) twenty-five hours after irradiation for thirty seconds at 250,000 volts. The cutaneous edema and hemorrhage are more marked than in rat 42.

about eight days had regained its normal texture, although the hair was not so abundant as before.

The rats irradiated for one second were killed with a blow on the head, six hours, six days, eight days and forty-nine days later, those given five seconds' irradiation, six days, eight days and forty-nine days later, those given ten seconds' exposure, after seventy hours, eight days and fifty days, those given fifteen seconds' exposure after twenty-five hours, four days, twelve days and twenty-one days, those given twenty seconds' exposure, after eight days, those given thirty seconds'

exposure, after twenty-five hours, twelve days and twenty-one days, respectively. Six animals were used as controls. The series, then, seems sufficiently representative of time intervals to give a reasonably comprehensive picture of the alterations in the testis under the conditions of the experiment.

In no instance was there observed any adhesion of the subcutaneous tissues to the tunica vaginalis. The testis when exposed in its sac was always smooth and glistening. In the rats given five-tenths, one-tenth,



Fig 2—Scrotal area (rat 39) eight days after irradiation for twenty seconds at 250,000 volts. A large necrotic and hemorrhagic area is present in the scrotum with slightly dry surface.

five and ten seconds' exposures, no gross changes were observed. In those given fifteen, twenty and thirty seconds' exposures, there was frequently, but not always, present a zone of translucency directly beneath the irradiated area, and occasionally punctate hemorrhages. With the heavier doses, there was visible edema of the tunicae, but no hydrocele. The epididymis showed no macroscopic changes. The testes when incised bulged out in a semi-diffuent manner, but this is the normal consistence in the white rat. The tissue was fixed in small portions in Zenker's fluid, neutral solution of formaldehyde-Zenker, a diluted

solution of formaldehyde, U S P (1:10), and according to Kolachev's osmic-bichromate method for the demonstration of the Golgi apparatus and lipoid and fat droplets

Before describing the abnormalities encountered in the testes of the white rats exposed to cathode rays, I must point out that in the so-called normal testis not only of the rat but of other mammals various degenerations are encountered. Barratt and Arnold,¹¹ in their study of lesions in the rat's testis caused by roentgen rays, described the following changes in their normal series: (1) necrosis of spermatocytes of the first order in a small fraction of animals, the cells taking basic instead of acid dyes, and being found both in cells undergoing mitosis and in those not dividing, (2) fatty globules near the

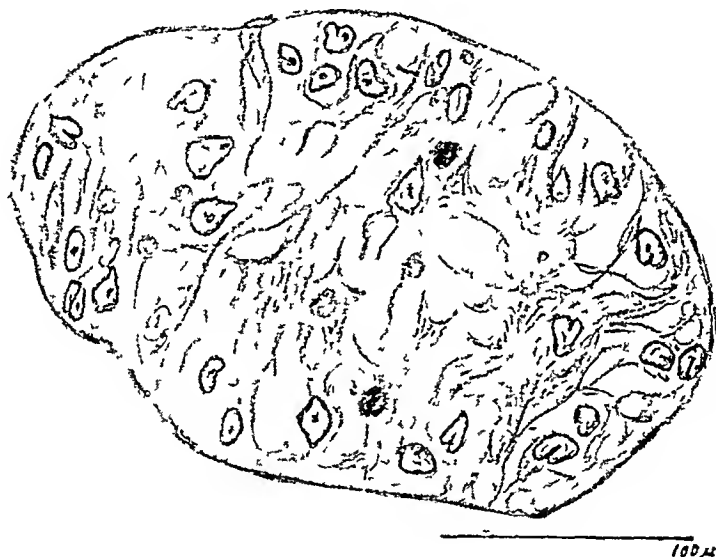


Fig 3—Seminiferous tubule thirteen days after the application of roentgen rays (copied from Barratt and Arnold *Arch f Zellforsch* 7 242, 1911-1912). All seminal cells have disappeared. Externally, the basement membrane is seen. Distributed within the tubule are numerous nuclei of cells of Sertoli, the cytoplasm of which forms a coarse framework, within the meshes of which fatty masses, more or less darkly stained with osmic acid, are sparsely scattered. No definite lumen is present in the tubule (compare with fig 7).

lumen of tubules, about 3 microns in size, in the cytoplasm of spermatids and in cast-off particles of cytoplasm, a dozen or more in a group, (3) fatty globules from 2 to 12 microns in size in young spermatids.

These changes were seen chiefly in the noncopulatory periods, when the testes were in the abdomen. Multinucleate cells rarely occurred and occasionally enlargement of archoplasmic vesicles. They did not encounter intranuclear body vacuoles or irregular mitoses.

¹¹ Barratt J O W, and Arnold G. Cell Changes in the Testis Due to X-Rays, *Arch f Zellforsch* 7 242, 1911-1912.

In my control animals, few degenerative changes were seen in numerous sections from both testes. No cell necroses were found, nor any multinucleate or giant cells of any type. Fatty globules, however, were not infrequently seen lying free in the lumen of tubules and sometimes in the spermatid zone. They were minute, and their significance was not clear.

The following observations were made on tissue fixed in Zenker's fluid and stained with hematoxylin-eosin and eosin-methylene blue.

One exposure of one-half second, at 200 000 volts, produced definite changes in the skin, and in six days repair was well under way beneath the zone of necrosis. Epithelial regeneration was definitely retarded, however. The tunica vaginalis testis was normal. The lymphatics

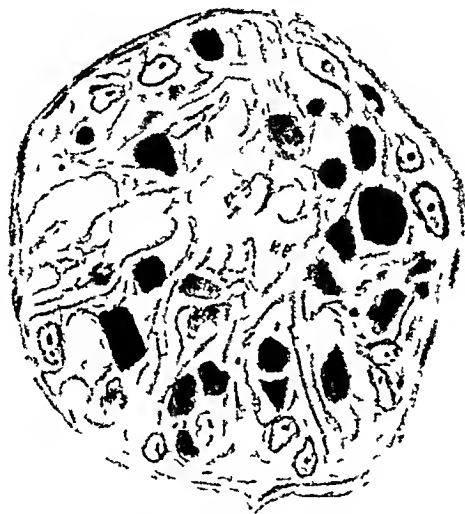


Fig 4—Seminiferous tubule eleven days after the application of roentgen rays (copied from Barratt and Arnold). The seminal cells have disappeared, their place being taken by numerous fatty masses stained in varying degrees of darkness by osmic acid. The nuclei seen are those of cells of Sertoli, the cytoplasm of which forms a loose meshwork throughout the tubule. The lumen of the tubule has become obliterated.

beneath the tunica were dilated. Blood capillaries occasionally showed endothelial proliferation, but no thrombosis. The seminiferous tubules were all intact. The interstitial cells appeared normal. The Sertoli cells and spermatogonia were unaffected. Many tubules showed hyaline droplets lying free in the midzone and also free in the lumen intermingled with mature sperm. These were probably seminal granules derived from degenerated spermatids. A few balloon-like vacuolated cells in some tubules along the periphery of the testis were probably degenerated spermatocytes of the first order.

Irradiation for one second gave a picture much like the foregoing, except that hyaline droplets were more numerous after six days. Often it appeared as though they represented altered heads of spermatozoa, the flagella having disappeared. Pyknosis in cells of spermatid type was prominent in some rats. An occasional atrophic tubule was found, but this could well be unrelated to the irradiation.

Irradiation for five seconds produced marked degeneration of the scrotum, but there was no distinct continuity of lesion between the subcutaneum and the tunica vaginalis. Lymphatic dilatation and some endothelial proliferation were present. Along the periphery of the testis, just beneath the scrotal skin, a few tubules were encountered in which the mature spermatozoa showed marked swelling of their heads, which took a pale basic stain. No tails could be demonstrated on many sperm.

The results in the series of rats given five seconds' exposure to 200,000 volt cathode rays may be summarized as follows. The tunica vaginalis was normal. The lymphatics were dilated. The tubules just beneath the capsule showed swelling and vacuolation of spermatids, with desquamation and fragmentation of cells. The Sertoli cells were normal. A dearth of mitotic figures in spermatogonia was noted. It was at times difficult to be certain of the identity of the many degenerated cells. Hyaline droplets were abundant in the lumen. Some phagocytosis of spermatozoa by large mononuclear cells was noted. The interstitial cells were normal and often contained a lipid pigment. The aforementioned alterations were visible in six days and as late as forty-nine days after exposure could still be detected. The number of tubules affected was small, but their location beneath the field of irradiation would seem to indicate that the changes were probably due to the irradiation. Most of the tubules showed abundant mitoses and spermatogenesis. The epididymis was usually full of sperm, but some cells of the lining membrane were swollen and vacuolated or undergoing a hyalovacuolar change.

So far the evidence of injury of the testis by the cathode rays has been entirely microscopic. However, with exposures of ten seconds and longer there were also gross alterations. Within twenty-four hours, areas of translucency appeared just beneath the capsule on the irradiated side, and occasionally punctate hemorrhages after fifteen or twenty seconds' exposure. The translucent foci were due to degeneration of tubules, the spermatozoa and most of the epithelium of which had undergone necrosis with disappearance of most cells after seven days. That it takes much less irradiation to produce effects in germinal epithelium than in connective tissues was evident in this series of animals. The tunica vaginalis and the underlying fibrous capsule showed no histologic change, while the seminiferous tubules were con-

siderably altered. In some rats a zone about five tubules or about 0.6 mm. deep was affected with a sharp line of demarcation between healthy and damaged tubules, that is, whole tubules were injured usually. In the rats exposed for fifteen and twenty seconds the depth of the injury was slightly greater and there was a more gradual diminution of visible lesions.

The sequence of changes seemed to be first swelling and vacuolar degeneration affecting the spermatids and spermatocytes. The sperma-

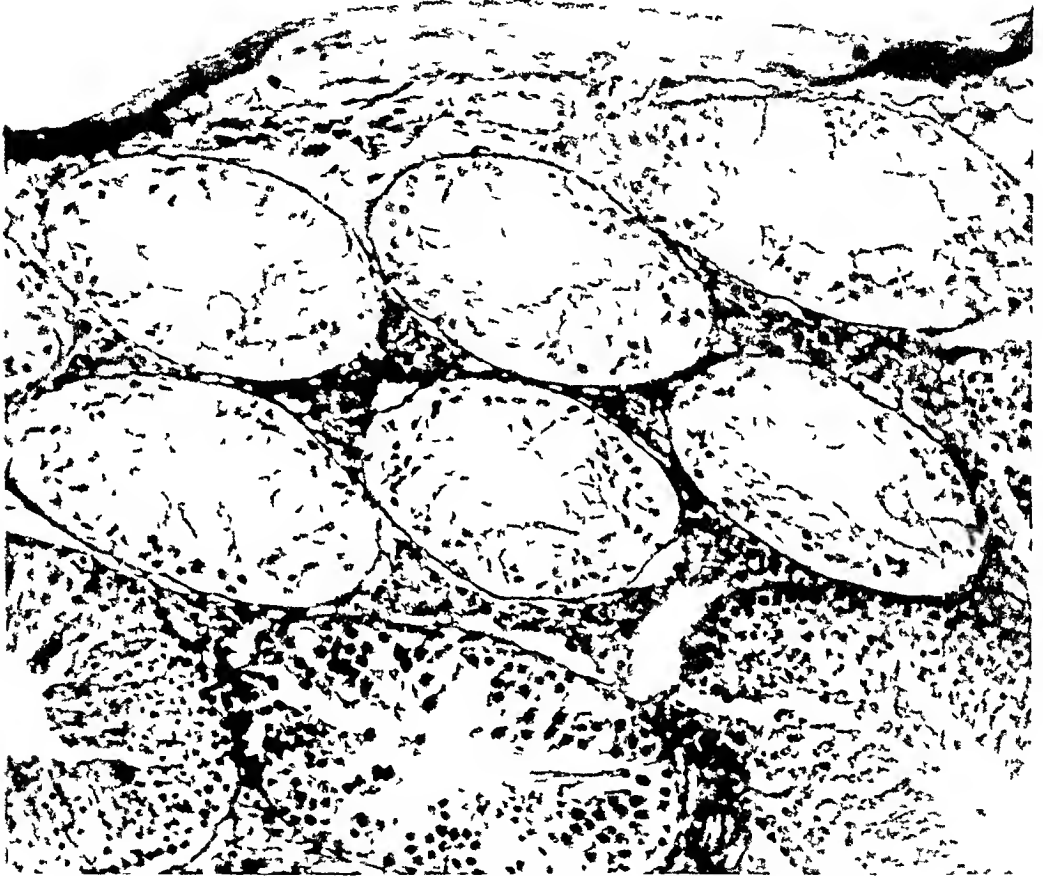


Fig. 5—Spermatic tubules to a depth of about 0.3 mm. in rat 38 after fifteen seconds irradiation of scrotal area at 250,000 volts showing loss of spermatogenic cells and proliferation of Sertoli's cells, $\times 154$

tozoa seemed more resistant. After four days, the damaged cells and spermatozoa had disappeared, and only shadowy outlines of cells remained. Even Sertoli's cells had been destroyed in some tubules. The changes in the nuclei were largely due to chromatolysis with or without preceding pyknosis. Intracellular vacuoles were found in spermatocytes and spermatids. After fifty days, large multinucleate phagocytic cells appeared and engulfed nuclear particles and heads of spermatozoa. Sertoli's cells almost filled the lumen of some tubules.

Obliterative proliferations of vascular endothelium were occasionally seen. In marked contrast to the tubules within the "zone of influence," other tubules in the same low power field appeared normal with spermatogenesis in progress and mitoses in about normal number and type.

The profound alterations in the germinal epithelium described were visible with the ordinary methods of fixation and staining. It was thought that finer cell changes might be detected by the use of other



Fig 6—Superficial tubules of testis in rat 39 eight days after twenty seconds' irradiation of scrotal area at 250,000 volts, showing destruction of spermatogenic cells, many multinucleate cells, some phagocytic, in two of the tubules, proliferation of Sertoli's cells, which tend to fill the lumen, and nuclear degeneration in many of Sertoli's cells, $\times 163$

technics. Special attention to certain structures in cytoplasm and nuclei seemed warranted. Gatenby and Wigoder¹² recently studied the effects of roentgen rays on the Golgi apparatus of the epithelium of the guinea-

¹² Gatenby, J. B., and Wigoder, S. The Effect of X-Radiation on the Spermatogenesis of the Guinea-Pig, *Proc Roy Soc* **104** 351, 1928

pig's testis Gatenby had previously concluded that the centrosome was not injured by roentgen rays, that strong doses prevented neither proper orientation of the spermatids in relationship to the lumen nor proper outgrowth of the flagellum from the head centrosome Gatenby and Wigoder summarized their work as indicating that the specific effect of roentgen irradiation on cell mitosis is due to a temporary breaking down of certain lipid substances necessary for mitosis This lipid substance was supposed to be located in the cortex of the Golgi



Fig 7—Degeneration of seminiferous tubules to depth of about 0.6 mm ($\times 138$) in rat 41 fifty days after ten seconds' irradiation of scrotal area at 250,000 volts Sertoli's cells tend to fill up the lumina and themselves show many changes There is dilatation of the lymphatics The tunica vaginalis is normal Vacuolation and fatty degeneration are prominent Compare with figure 3

apparatus They found that sometimes the Golgi lipid cortex became flocculent and granular instead of smooth The most radiosensitive period of mitosis was just before the prophase, since it was impossible for the cell at that stage to recover from the effects of broken down lipids, an abnormal mitosis leading to death resulting Cells entering mitosis might be killed by inability of the centrosome to pass out of

the idiozome preparatory to amphiaster formation Postnuclear bodies were sometimes abnormal in the irradiated testis

The rats in my series exposed for ten, fifteen, twenty and thirty seconds to rays, at 250,000 volts, and a current of 1 milliampere, were killed by a blow on the head The testes were removed at once, and portions placed in various fixatives Small pieces were fixed according to the Kolachev-Nassanow method for the demonstration of the internal reticular apparatus of Golgi, an osmic acid treatment combined with bichromate-chromic acid fixation The Golgi apparatus becomes blackened by this method as do fat droplets and lipid bodies to a certain extent It is best to emphasize that errors in technic are easily committed in staining the Golgi apparatus, the most accurate observations of it being made by biologists who have had considerable experience with the various technics The material may be demonstrable by one method and not by others, hence it is usually advisable to try several before pronouncing on the characteristics of the Golgi apparatus It is generally considered that the Golgi apparatus is relatively easily demonstrated in the testis by osmification, and Kolachev's technic was used successfully by Gatenby and Wigoder in their studies of roentgen changes in the guinea-pig's testis, hence the observations to be reported here are based on this method

In the control animals, the Golgi apparatus was usually well shown, hence, I feel, notwithstanding my small experience with this cell structure, that the changes to be described were real in the sense of at least occurring ante mortem and not being due to operative trauma or autolytic processes

The tubules that showed the most degeneration with ordinary staining methods disclosed varying degrees of alteration of the Golgi apparatus Fragmentation with dispersion of the particles rather widely throughout the cytoplasm was a common picture, although where the nucleus had been destroyed no trace of Golgi material was found The cells of Sertoli appeared the least affected as judged by the morphology of the Golgi apparatus

The acrosome of the spermatid was markedly enlarged twenty-four hours after thirty seconds' irradiation, and the Golgi material often appeared more or less fused with it The nucleus was frequently surrounded entirely by a ring of blackened fine granules, even in cells that were normal otherwise In spermatocytes similar changes were noted More normal-appearing Golgi networks were seen in the more deeply situated tubules indicating that the penetration of the rays was not deep Some spermatogonia showed a Golgi apparatus resembling a spherical vesicle with a central clearer zone This might be normal as to shape, but often seemed considerably increased in size

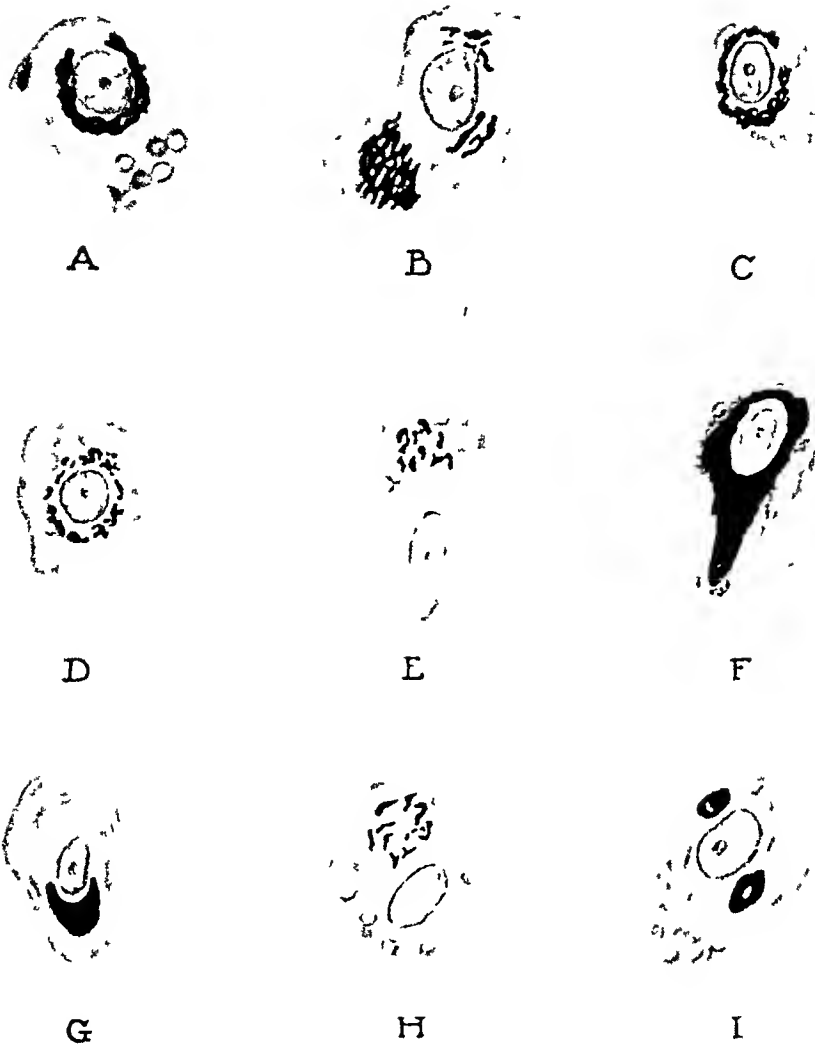


Fig 8—Drawings of various cells of the rat's testis following exposure to cathode rays. Kolachev's osmic acid technic was used for the demonstration of the Golgi apparatus. *A*, *C* and *D*, spermatocytes of the first order showing perinuclear arrangement of Golgi material in rat 43 after thirty seconds' irradiation of the scrotal area at 250,000 volts, in *D* fragmentation has occurred. *B*, an osmiophilic network and rodlike and granular bodies isolated from a larger mass lying close to the nucleus. *E*, a spermatid with fragmented Golgi material. *F*, a cell from the midzone of a tubule, possibly representing fused Golgi and acrosomic material. *G*, probably a spermatid, from rat 42 twenty-five hours after irradiation for fifteen seconds at 250,000 volts, showing enlarged archoplasmic vesicle and no definite Golgi network. *H*, fragmented Golgi material, numerous lipoid droplets (rat 42). *I*, cell of doubtful identity, showing separation of Golgi material into two portions, each somewhat spherical and vesicular.

The interpretation of alterations of what might be considered the normal type of Golgi network for a given cell must be accompanied by many qualifications. Cowdry,¹³ in particular, emphasized the need of great caution in evaluating such changes. He found the term "apparatus" objectionable because it carries with it the idea of a mechanism. He stated that in *Metazoa*, taken generally, the Golgi apparatus shows a tendency to occur in isolated rods and spherules instead of complicated networks, this being particularly true in stages of oogenesis and spermatogenesis. Occasionally, isolated fragments are met with in *Protozoa*, some writers hence using the term Golgi "body." This, however, gives the impression of distinctive form and to some extent of solidity, as contrasted with the relative fluidity of the Golgi material.

Hyman¹⁴ in his study of the spermatogenesis of *Fasciolaria* found that the Golgi apparatus of the germ cells and certain somatic cells occurs in the form of tiny spherule-like vesicular bodies with a central "chromophobe" and a peripheral "chromophil" substance. The more complicated networks are apparently encountered higher up in the animal scale.

Cowdry¹³ reviewed the literature on the morphology of the Golgi apparatus under various abnormal conditions which included tumors, tuberculosis, rabies, experimental poisoning and vitamin deficiency. The most common observation was fragmentation. Dispersal throughout the cytoplasm, perinuclear formations, increase in size, reduction in size and reversal in position are reported, but no one change pathognomonic of a given condition.

In my rats exposed to cathode rays, swelling was a common abnormality of the Golgi apparatus, also fragmentation and perinuclear arrangements. Legendre¹⁵ in 1910 electrically stimulated the posterior root lumbar ganglion of a dog and found fragmentation with dispersal to the periphery of the cytoplasm. Cajal¹⁶ found that autolysis produced fragmentation.

That the exposure of the rat's testis to cathode rays causes definite changes in the Golgi apparatus of the germinal epithelium is suggested by my experiments. Gatenby and Wigoder found that in the testis of the guinea-pig irradiated with roentgen rays the lipid cortex becomes flocculent and granular. The other degenerative and necrotic changes seen in the testis of the rat exposed to cathode rays seem very

13 Cowdry, E. V. General Cytology, Chicago, University of Chicago Press, 1924, chapter on Cytological Constituents.

14 Hyman, O. W. Spermic Dimorphism in *Fasciolaria Tulipa*, J. Morphol. **37** 307, 1923.

15 Legendre, quoted by Cowdry (footnote 13).

16 Cajal, quoted by Cowdry (footnote 13).

similar to those found by Barriatt and Arnold in their rats irradiated by roentgen rays. Hence it seems warranted to say that the effects of roentgen rays on germinal epithelium, as well as on the skin and subcutaneum, are probably due not to roentgen rays per se but to the electrons or cathode rays set free in the tissues.

These studies suggest that cathode rays applied to the abdominal wall of female rats might in a similar manner produce changes in the ova. Experiments with fertility should also be made for further comparison with the well known effects of irradiation with roentgen rays.

SUMMARY

A study was made of the effects of cathode rays of high voltage on the germinal epithelium of the male adult white rat. The shaved scrotal area was exposed in front of the anodal window of the Coolidge cathode ray tube at voltages of 200,000 and 250,000 with a current of 1 ma. The length of the exposure varied from five-tenths second to thirty seconds.

The changes in the scrotal skin were similar to those in the abdominal skin as described previously by Waddell and me.

Definite lesions were produced in the seminiferous tubules in a zone about 0.6 mm. in depth. The lesions consisted of degenerative and necrotic changes resembling those caused by roentgen rays. The tela subcutanea below the upper 0.2 mm. of the skin and the tunica vaginalis testis showed no evidence of injury, indicating clearly the much greater sensitivity of germinal epithelium to this form of irradiation. Alterations in the Golgi apparatus of the germinal cells were also observed, which correspond with the observations in the testis of *Cavia cobaya* irradiated with roentgen rays, as reported by Gatenby and Wigoder.

These observations are offered as further biologic evidence that the effects of roentgen rays are not due primarily to the roentgen rays but to the electrons or cathode rays set free in the tissues.

OSTEOGENESIS IMPERFECTA CONGENITA

A STUDY OF ITS HISTOPATHOGENESIS *

M WEBER, M D

SAN FRANCISCO

The progress made in the histology of normal and pathologic bone within the last decade encourages a renewed investigation of the histopathogenesis of osteogenesis imperfecta. According to von Recklinghausen,¹ thirty cases of osteogenesis imperfecta (osteopsathyrosis congenita or fragilitas ossium congenita) were known in the literature to 1910. This number has been greatly increased within the last twenty years by the utilization of the roentgen rays in diagnosis. It is superfluous to review here the papers which may be found in the literature of the various countries, since that has been done recently by Dietrich.² The clinical and roentgenologic picture of osteogenesis imperfecta is well known. Therefore, a purely descriptive case report is no longer justified.

The cause of the disease is as obscure as the clinical and roentgenologic aspects are obvious. The theories concerning its cause (i. e., disturbances of internal secretion) are proved by neither morphologic nor biochemic observations. "The assumption of a pluriglandular deficiency," said Dietrich, "is a conception without foundation." Since the etiology is unknown, we have also no rational therapy.

Knowledge of the pathogenesis of the disease is intermediate to the well known clinical picture and the totally unknown cause. Only few definite facts have been added recently to the older knowledge of the histogenesis, since the classic work of von Recklinghausen. All authors have agreed that a lack of osteoblasts (a dysfunction, Bauer³) characterizes the histologic picture. But there is not a complete lack of bone, but rather a tissue of inferior quality. The question arises whether this inferiority must be traced to an original "vitium primae forma-

* Submitted for publication, Nov 7, 1929.

* This study was aided by grants from the John C and Edward Coleman Memorial Fund.

* From the George Williams Hooper Foundation for Medical Research, University of California.

1 Von Recklinghausen, F. Untersuchungen über Rachitis und Osteomalacie, Jena, Gustav Fischer, 1910, p 472.

2 Dietrich, A. Die Entwicklungsstörungen des Knochens, in Henke-Lubarsch Handbuch der speziellen Pathologie und pathologischen Anatomie, Berlin, Julius Springer, 1929, vol 9, p 198.

3 Bauer, K. H. Ueber Osteogenesis imperfecta, Deutsche Ztschr f Chir 154 166, 1920.

tions" (Kaufmann⁴ Dieterle⁵ and Sumita⁶) or to disturbances which influence the bone-forming tissue secondarily. In any case, the lack of bone tissue, as well as the pathologic changes in the bone tissue actually present, is an expression of the underlying cause. The histologic features of the bony system represent an angle from which the problem must be tackled. Thus, one sets the question "How" before the question "Why."

In this deductive, analytic procedure, I shall be guided by the following considerations in regard to the complicated structure of bone, in general. Bone tissue is a local conglomeration of elements which represent the single time phases of the development of bone. Since knowledge of the normal is the foundation for the understanding of pathologic changes, the conglomerate of normal bone ("normal bone picture") must be separated into its time components. These components arranged according to their phylogenetic and ontogenetic appearances represent the "normal bone-building system," the general principles of which I have attempted to show in a previous paper.⁷ Pathologic bone tissue represents a quantitative and qualitative caricature of the normal, and also a repetition—though modified—of the single stages of normal development. Thus, the single phases of the normal bone-building system must be balanced against those of the pathologic bone. Before this can be accomplished, the pathologic bone structure ("pathologic bone picture") itself must be divided into its time components.

Summarized, the question as to the pathogenesis of osteogenesis imperfecta may be stated as follows: "How have the time phases of the normal bone-building system changed quantitatively and qualitatively in order that the local conglomerate of the pathologic bone structure—as observed in osteogenesis imperfecta—might come about?"

The investigations were based on a case of osteogenesis imperfecta in a 2 day old girl recently observed, which will first be reported briefly.

REPORT OF CASE

History—Both parents were strong and healthy with essentially negative family histories. It was their first child. The pregnancy was normal, the

⁴ Kaufmann, E. Pathology, translated by Reimann, Philadelphia, P. Blackiston's Son & Company, 1929, vol 2, p 1176

⁵ Dieterle, T. Die Athyreosis, Virchows Arch f path Anat **184** 111, 1906

⁶ Sumita, M. Beitrage zur Lehre von der Chondrodystrophia foetalis (Kaufmann) und Osteogenesis imperfecta (Vrolik), Deutsche Ztschr f Chir **107** 1, 1910

⁷ Weber, M. Bone Pathology and Its Relation to the Problem of Otosclerosis, Ann Otol Rhin & Laryng **37** 1232, 1928

mother having medical supervision and direction in diet. The delivery was normal and at term. The child was weak and cyanotic. An abnormal skull and head were noted. Therefore, roentgen examination was made. The report of the roentgenologist, Dr. E. Schulze Heald, read as follows: "Osteogenesis imperfecta with many old and recent fractures of long bones and ribs. Very imperfect ossification of the skull." Each successive roentgenogram before and after death revealed more fractures. The cyanosis became greater, and the weakness more accentuated. Death probably was due to progressive asphyxiation. The body was preserved by the injection of formaldehyde through the left ventricle and by submergence in formaldehyde and was given to me for autopsy. (Dr. E. Schulze Heald, roentgenologist, Alta Bates Hospital, Berkeley, Calif., turned this case over to me for microscopic examination.)

Habitus—The weight of the body was 5 pounds (2.3 Kg.). The soft parts were well developed. The subcutaneous fat was abundant. The extremities were extremely bowed, the lower extremities so much so that the plantar surfaces of the feet were approximate. The extremities were plump, but not malformed. They showed abnormal motility accompanied by marked crepitation. The neck appeared short. The appearance of the head suggested a bitemporal swelling. The growth of hair was conspicuously abundant. The skull felt like a rubber ball (Hildebrandt⁸). The capsule was thin, like parchment.

Organs—Autopsy of the cavities of the body did not reveal any special abnormalities. The development of the organs was normal relative to the age, and there were no macroscopic pathologic changes. The following organs were examined microscopically: thymus, heart, lungs, liver, gallbladder, spleen, suprarenal glands, kidneys, pancreas, uterus and ovaries. The examination of the specimens was made difficult by the aforementioned injection of formaldehyde. There was, however, a hyperemia of all organs and, besides, much hemosiderin, as was demonstrated by the Turnbull-blue reaction. Otherwise, the organs did not reveal any special microscopic changes.

General Observations in the Bone System—The calvarium was easily dissected by means of scissors. The frontal and occipital bones were harder and from about 1 to 2 mm. thick, while the remaining part of the calvarium was almost purely membranous. Smaller and larger bony islands were embedded in this membranous capsule. Holding the calvarium to the light, these islands revealed an astral structure, like ice flowers. The space between the islands was translucent. Autopsy of the brain itself showed no macroscopic abnormalities.

The long bones were separated with great difficulty from the soft parts. The bones revealed many fractures, which may be seen well in the x-ray plate. One dealt here partially with fresh fractures (i. e., sixth and seventh left ribs and fifth right rib, left scapula, left humerus), partially with old fractures with more or less well developed callus formation (i. e., ninth and tenth left ribs, sixth, seventh, ninth and tenth right ribs, left radius, left ulna, right humerus and both femora). Several ribs were fractured twice. The fresh fractures were without doubt of postmortem origin, the older fractures evidently occurred in utero, as may be concluded from the large quantity of callus.

In general, longitudinal sections of the long bones presented an identical picture which differed only by the special features of the fractures. The conditions will be discussed, those in the right femur being used as an example (fig. 1). The isolated bone was elastic and flexible as rubber. There was no continuity of the cortex. Also a real spongiosa was not present. The bone may

⁸ Hildebrandt, H. Ueber Osteogenesis imperfecta, Virchows Arch. f. path. Anat. 158:427, 1899.

be compared with a soft tube of periosteum (extending between the two epiphyses) which is studded internally with splinters of bone. The marrow was conspicuously red. In the line of fracture, there was a fissure, lined proximally and distally with white tissue which microscopically proved to be cartilage, thus indicating a pseudo-arthritis. The proximal epiphyseal line was straight, the distal, gently curved. The cartilage of the distal epiphysis had an ossification center which was large, if one considers the age of the child. Let me emphasize that the incomplete formation of a cortex, as well as the straight osteochondral junction, repeated itself in all the long bones inclusive of the ribs, in the same manner.

THE DIAGNOSIS

In order to be able to diagnose osteogenesis imperfecta, according to von Recklinghausen¹ a triad of symptoms must be demonstrated.

1 "The fissures and fractures of the skeleton must have occurred repeatedly." In our case, this postulate was easily fulfilled. Numerous old and new fractures dominated the picture.



Fig. 1—Longitudinal section through the right femur. Periosteal tube between the epiphyses, studded interiorly with bone splinters. Ossification centers in distal epiphysis. Straight epiphyseal line. Pseudo-arthritis in the middle of the diaphysis.

2 "The fractures must have occurred in early life and must be traceable into the intra-uterine period." Since the child under discussion was only 2 days old, and many of the fractures revealed abundant solid callus formation, it may be concluded that this requirement of von Recklinghausen was also fulfilled.

3 "There must be such structural conditions of the bone as will account for the spontaneity of the fractures." It has been seen that the bone formation as a whole in the case under consideration was so imperfect that one could not speak of a spongiosa, and could speak of a cortex only in a limited sense. The calvarium was almost purely membranous, showing only discrete centers of ossification. The details of the bone structure will be treated in the following chapter. Without doubt, it will become still more evident that this factor was also present.

In brief, the diagnosis of the roentgenologist may be confirmed. One is dealing with a typical case of osteogenesis imperfecta.

THE HISTOLOGIC STRUCTURE OF THE BONE IN THIS CASE

The Osteochondral Junction—As may be concluded from the examination of a great number of specimens all osteochondral junctions presented, in general, the same picture. I shall describe the conditions found in the fourth right rib, which were typical (fig 2). The epiphyseal line was almost always straight. The columns were for the most part regular, occasionally, though, there were several columns in one block, surrounded by intercellular substance. The opening up of the cartilage always occurred in a normal manner. The intercellular substance between the columns showed a normal degree of calcification. Nowhere was there a superabundance of uncalcified cartilage as in the case of rickets, nor was



Fig 2—Osteochondral junction of the fourth right rib. No particular disturbance of the cartilage. Regular opening up. Free cartilage splinters, well calcified. No bone deposition on the same. Superabundance of lymphoid marrow. Specimen fixed in collodion, stained with hematoxylin-eosin. Leitz Objective 1, eyepiece 4 x, extension 51 cm, magnification 261 1.

there a true rosary. The deposition of bony substance on the cartilaginous remnants was minimal or even completely lacking. As a result of this, there was no continuous framework of spongiosa. Rather, the cartilaginous remnants lay as free splinters in the marrow. Besides, they often lay at right angles to the long axis of the bone, i. e., they paralleled the epiphyseal line, as observed for instance in the right ulna (fig 3). Wherever bone had been deposited on the cartilaginous remnants, it stained blue with hematoxylin and was evidently well calcified. There was no sign of a lamellar arrangement.

The cortex—A transverse section through the long bone (e g, the tibia) gave a good idea of the construction of the cortex. A cross-section of the tibia was decalcified for twenty-four hours in 5 per cent nitric acid, embedded in paraffin, cut 10 microns thick and stained with hemalum-eosin or Van Gieson's stain. Viewed under low power (fig 4), it became evident that the cortex consisted only of a loose framework, thus resembling a spongiosa. Some of the splinters lay entirely free. In such areas, there was no bone separating the marrow from the periosteum. A conspicuously fibrous periosteum surrounded the framework. The marrow was present in much greater abundance than bone tissue. Viewed under higher magnification, the cortex showed the following details (fig 5)



Fig 3—Proximal osteochondral junction of the left ulna. Crosswise position of the cartilage splinters in the lymphoid marrow. Minimal fiber bone formation under the periosteum. Specimen fixed in collodion, stained with hematoxylin-eosin. Leitz. Objective 1, eyepiece 4 \times , ext 50 cm, magnification 2561.

Toward the lumen, there was a marrow consisting of lymphoid elements. Toward the periphery were situated islands of peculiar bone tissue. These islands, surrounded by a loose fibrous tissue, showed a dark blue marginal zone after hematoxylin-eosin staining. The inner area of the islands appeared lighter. Occasional darker spots, however, could be observed, as well as granular crumbly regions, which occur not infrequently in cases of irregular and pathologic calcification. Often the entire bone structure of the cortex was fragmentary and scaly (fig 6). The bone cells were monstrous and plump. After being stained with thionin-picric acid, these cells showed only thick and short canaliculi. Besides, they lay irregularly. A lamellar arrangement could not be observed.

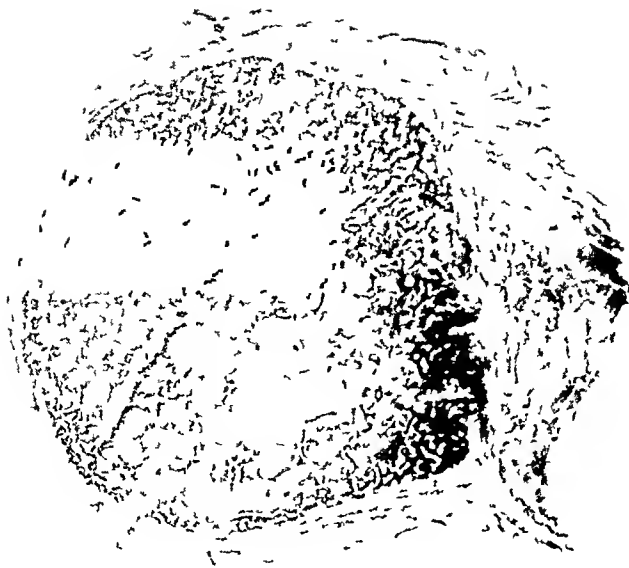


Fig 4—Transverse section of the diaphysis of the right tibia. Lack of spongiosa. Loose cortex consisting of splinters of fiber bone surrounded by a dense fibrous tube of periosteum. Gelatin. Frozen section. Hemalum-eosin. Leitz. Summar 80, ext 77.5 cm, magnification 9.1

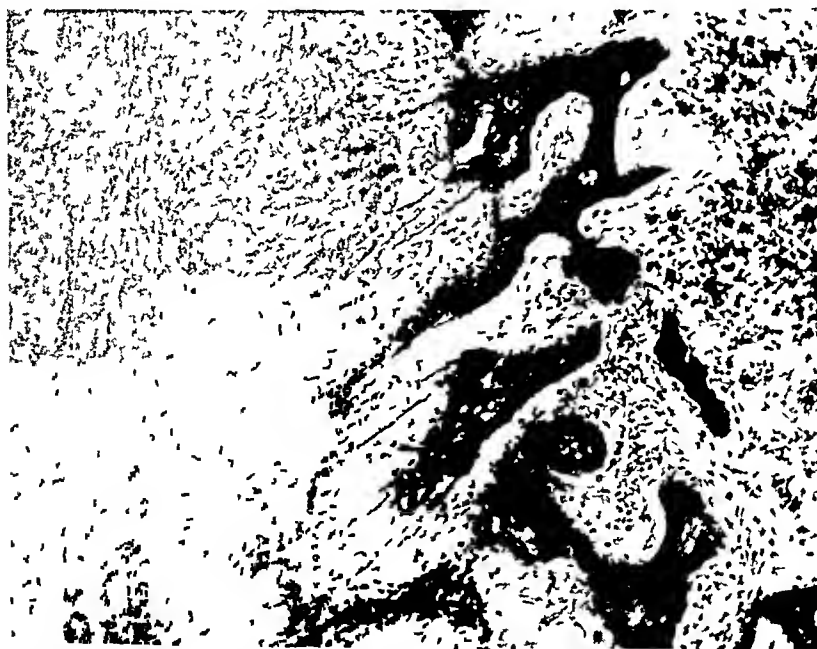


Fig 5—The same specimen as shown in figure 4, under higher power. Internally, lymphoid marrow. More peripherally, calcified fiber bone surrounded by reticulated and fibrous marrow. Under the periosteum, islands of fibroblastic osteoid surrounded by fibrous marrow. Toward the upper margin of the picture, dense periosteum. Parow's. Iron-hematoxylin, van Gieson's stain. Leitz. Objective apochromate 16 mm, eyepiece 4x, ext 40 cm, magnification 76.8.1

After staining with van Gieson's stain, one observed that fibers crossed each other within the islands. One dealt with a coarse fiber bone.

Toward the marrow cavity, this fiber bone was well calcified, though irregularly. Toward the periosteum, a younger stage of fiber bone was observed in which the calcification was still, in part, completely lacking. This young bone tissue appeared at first in the form of islands, which were connected by coarse fibers, on the one hand, with the cambium layer of the periosteum and on the other hand with the older, already calcified, fiber bone. These young stages gave an excellent opportunity for studying the modus of fiber bone formation (fig. 7). The intercellular substance increased between the cells, without the aid of osteoblasts arranged in an epithelial row. The cells enclosed by the inter-



Fig. 6—Same specimen as shown in figures 4 and 5. Fiber bone of the cortex under high power. Sealy and granular-crumbly appearance of the intercellular substance. Large vesicular cells. No active endosteum in the vicinity. Parowax. Hemalum-eosin. Leitz. Objective 6 a, eyepiece 4 x, ext. 51 cm, magnification 357.1.

cellular substance remained lying in their original position and seemed passive. Their morphologic appearance did not change, except for a slight rounding off of the outline of the cell. The intercellular substance stained red with eosin. The islands must be regarded as "fibroblastic osteoid," which is the preliminary stage in the formation of fiber bone.

A detailed examination of all important bones of the skeleton revealed that the entire bone system was formed by such fiber bone. It was not normal, however, but rather pathologic in its appearance, probably as a result of changes in the intercellular substance, as indicated by the blue color after hematoxylin-eosin staining.

Summarizing, one concludes that in this case the whole bone system consisted of pathologic fiber bone, which partially was still in a relatively low stage of development

The Fractures—The fresh fractures had little interest for these investigations Hemorrhagic foci, inclined to organization and hyaline transformation, had arisen between the fragments The designation "fragment" could be used often only in a limited sense, since not always a real fracture had occurred Indeed, the bone tissue was in some places so lacking in continuity that even without a "fracture," the slightest movement (Bauer,³ Harbitz,⁹ von Recklinghausen¹) might produce a hemorrhage with all its consequences The majority of these so-called fractures were in reality "pseudofractures"

The older fractures and pseudofractures already showed reactions of the bone-building system A good example for studying these changes was offered by

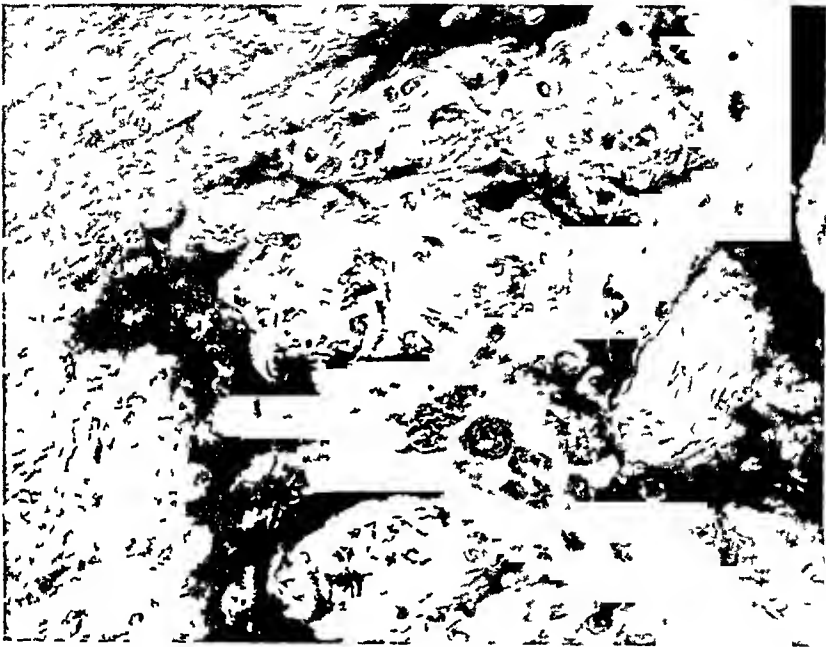


Fig 7—Same specimen as shown in figure 4 Beginning of fiber bone formation, fibroblastic osteoid Inclusion of the cells of the fibrous tissue in situ by increase of intercellular substance, later calcifying No osteoblasts in rows Collodion Iron-hematoxylin, van Gieson's stain Leitz Objective 6 a, eyepiece 4 x, ext 40 cm, magnification 280 1

the fractures of the left forearm, in which the x-rays (fig 8) indicated an enormous callus formation Viewing with middle power, one observed that a new formation of cartilage and bone had occurred in the region of the fracture (fig 9) The cartilage islands were easily distinguished by their light color, after being stained with thionin-picric acid (fig 10) These cartilaginous portions had evidently originated from the periosteum, as well as from the marrow cavity Distal to these cartilaginous new formations there was a fissure, which was limited by new-formed bone

⁹ Harbitz, F Ueber Osteogenesis imperfecta, Beitr z path Anat u z allg Path **30** 605, 1901



Fig 8—Roentgen picture of the left arm showing fresh fracture of the humerus and old fractures of the radius and ulna with abundant callus (x-ray picture supplied by courtesy of Dr E Schulze Heald)



Fig 9—Longitudinal section of the left ulna Callus formation New formation of cartilage and fiber bone Collodion Hematoxylin-eosin Leitz Objective 1, eyepiece 4 x ext 50 cm, magnification 256 1

The examination of the detailed development and structure of the cartilage showed that the cartilage had arisen, after the manner of the fiber bone, from the loose mesenchymal tissue of the periosteum and marrow. Here, also, the intercellular substance played an important role (chondroid). But the cells, too, had undergone changes, from a spindle cell appearance to a more round and vesicular form. Aside from this, there were certain transitional areas in which neither the form of the cells nor the intercellular substance revealed whether one is dealing with osteoid or chondroid.

The new formation of bone tissue was increased in the neighborhood of the fractures (fig 10). There was a remarkable thickening of the cortex, whereby the real callus was produced. However, this cortex, too, was loose. It continued, centripetally, to a spongiosa which was conspicuously dense. Thus there



Fig 10—Longitudinal section of the left radius. Abundant formation of cartilage in region proximal to the fracture (light color). Also intensive new formation of fiber bone. Fissure, a probable pseudo-arthritis. Collodion Thionin-picric acid (Schmorl). Lantz Objective 1, eyepiece 4 x, ext 50 cm, magnification 256 1.

was no structural difference between the loose cortex and the dense spongiosa. The whole bone tissue surrounding the fracture, also, consisted of fibroblastic bone (fiber bone). Only at one point, an island of fiber bone was covered with one or two layers of lamellar bone, lined with osteoblasts in epithelial arrangement. This margin stood out clearly after the section had been stained with thionin-picric acid. Its bone cells were arranged neatly, paralleling the lamellae, and showed graceful dendritic canaliculi. The remaining portion of the callus showed the same absence of lamellar margins as did the skeleton in general. Where osteoblasts in epithelial rows covered the bone, there were a few discrete giant cells which resorbed the new-formed cartilage, as well as the bone by

lacunar resorption. Let me here emphasize that the callus tissue was the only place in which osteoblasts in rows and osteoclasts could be observed. Neither in the petrous bone nor in the vertebrae could a single osteoclast be found.

The Marrow—There were two types of marrow, a lymphoid and a fibrous (fig 5). The incidence of these two forms was limited to definite areas, in general, the lymphoid marrow predominated.

The lymphoid marrow filled the entire marrow cavity of the bone and the center of the spaces between the splinters of the cortex. There was a great variety of cells. Besides lymphoid and myeloid elements there was a number of eosinophils and nucleated reds (fig 11). Hemorrhages also were observed.

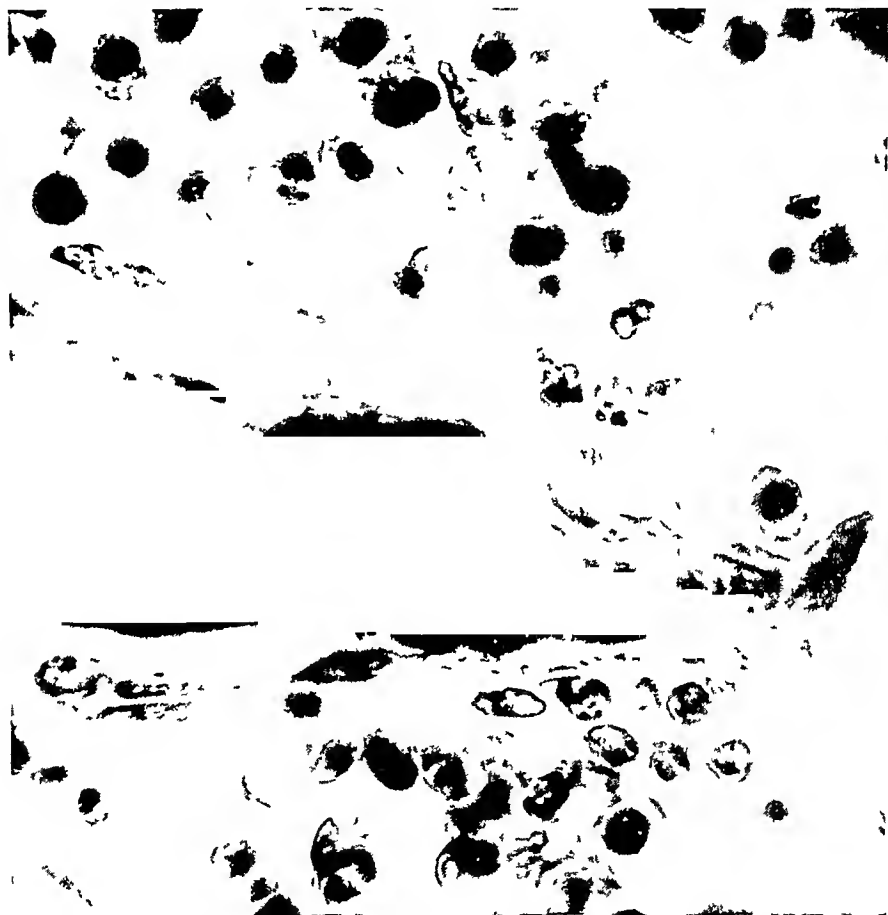


Fig 11—Bone splinters lying in the marrow cavity, surrounded by long spindle cells. Various types of cells in the marrow—myeloid and lymphoid elements, eosinophils and nucleated reds. Parowax. Hematoxylin-eosin. Leitz. Objective oil immersion apochromate 3 mm, eyepiece 4 \times , ext 85 cm, magnification 918 \times .

In some cases, this marrow reached directly to the bone splinters, which took the place of true spongiosa. In the osteochondral junction, also, this marrow continued to the epiphyseal line.

The fibrous marrow was observed (1) in the centers of the loosened cortex (to the extent that they were not filled in the center with lymphoid marrow), as illustrated in figure 5, (2) toward the periosteum (fig 7), and (3) within the great marrow cavity directly surrounding the bone splinters (fig 11). This

marrow resembled young mesenchymal tissue with its astral mother cells, which are connected by their extremely delicate fibrils. Lymphoid elements were disseminated throughout this tissue. Toward the great marrow cavity, this tissue gradually continued into the reticulum of the latter. While the fiber marrow became loosened toward the lymphoid marrow spaces, it became more dense toward the bone. Especially dense and purely fibrous was the tissue underneath the periosteum and within the marrow cavity of the callus. At those places where fibroblastic bone formation occurred, one might observe that these cells became more rounded (fig 12). An intercellular substance appeared, in which the fine fibers became embedded. From here, the fibers radiated into the reticulum not yet condensed. When a fibroblastic osteoid had appeared, it remained surrounded by a loose network of spindle cells (fig 11). Also, the cartilaginous remnants were covered with such loose fibrous tissue.

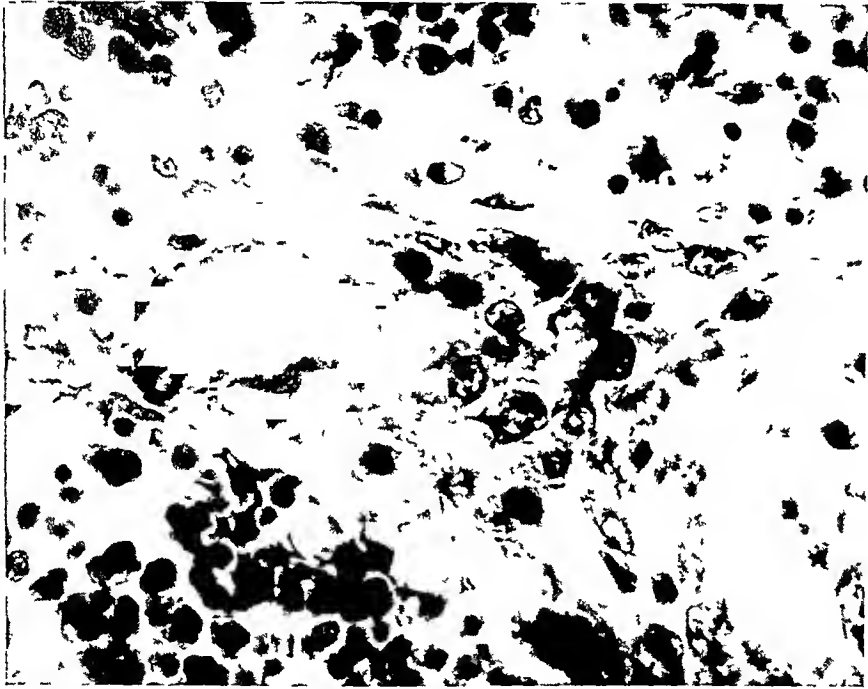


Fig 12—Fibroblastic bone formation in the marrow cavity. Rounding off of the astral mother cells of the reticulum. Increase of the intercellular substance. No osteoblasts in rows. Parow's. Hematoxylin-eosin. Leitz. Objective 6 a, eyepiece 4 x, ext 85 cm, magnification 597.1

THE PRINCIPLES OF THE NORMAL BONE-BUILDING SYSTEM

The knowledge of the single phases of the normal bone-building system is the foundation for the conception of the bone changes observed in osteogenesis imperfecta. Therefore, these phases of normal bone development will be discussed briefly. I presented them in detail about a year ago.⁷ In accordance with newer knowledge, one must recognize five stages, each distinguishable by the individuality of its morphologic picture.

1 *The Undifferentiated Mesenchymal Tissue*—The mesenchyme, after its development from the omnipotent germ, possesses only a pluripotent character. It is represented, as far as bone is concerned, by a loose reticulum, the so-called "reticulated marrow." The mother cells have an astral form and are connected by fine fibrils. This stage is the fundamental phase of the bone-building system.

2 *The Differentiation and Increase of the Inter cellular Substance*—The mesenchymal tissue differentiates in two directions. On the one hand, a fibrous tissue (fibrous marrow) originates containing long spindle cells, which soon are embedded in a homogeneous, hyaline matrix, staining red with eosin. The cells of the fibrous tissue are enclosed in situ, whereby they are slightly forced apart and rounded up. They lie irregularly in the increased intercellular substance. This stage is preliminary to the formation of fiber bone, one is dealing with "fibroblastic osteoid." On the other hand, more vesicular cells differentiate from the mesenchymal tissue, which are embedded in intercellular substance staining reddish blue. One is dealing here with "chondroid," the precursor of cartilage formation. If the formation of cartilage is completed, the intercellular substance stains almost pure blue with hematoxylin-eosin. It is plausible that, under pathologic conditions, a transition (so-called metaplasia) of one of these preparatory stages into another takes place by changes in the composition of the intercellular substance. Normally, this tissue has already unipotent character, which manifests itself in the development of the next stage.

3 *The "Nucleus" Formation*—The two intercellular substances of the preliminary stage become calcified. Both products represent the foundation for the later deposition of lamellar bone. Thus, two "nuclei" originate: (1) the "connective tissue nucleus" or "fibroblastic nucleus," i. e., the fiber bone, and (2) the "cartilaginous nucleus," i. e., the calcified cartilage. The structure of cartilage is generally known. It represents the model for the form of the most quickly growing bones. In principle, the structure of fiber bone is as follows. Its intercellular substance stains red or bluish red. The bone cells lie irregularly. They are plump and have short, thick canaliculi, which can be demonstrated only with difficulty by the thionin-picric acid method. This fiber bone is phylogenetically and ontogenetically the oldest type of bone. In general, there are three places where fiber bone may be observed: (1) as the "nucleus" of the bones preformed in membrane, (2) presumably as the first deposition of bone under the periosteum, and (3) invariably in the tendinous insertions.

4 *The Shell Bone Formation*—The lamellar bone (shell bone) is deposited on the previously formed "nuclei." In this process, cells participate which are arranged in an epithelial row. These osteoblasts

stand in close relation to the blood vessel system. Presumably, they originate from the endothelial cells of the blood vessels. These cells rise on edge to a vertical position, with relation to the bone. They have a basophilic plasma, and their nuclei lie basally and show no definite chromatin structure. Before the lamellar bone is deposited, the "nucleus" previously formed, becomes vascularized in many cases. This vascularization is well known, especially in regard to the "cartilaginous nucleus." Thus, the cartilaginous model is hollowed out. The "fibroblastic nucleus," however, from the start, has enclosed blood vessels, which makes a separate process of hollowing out unnecessary. These conditions may be well recognized in the calvarium. The lamellar bone deposited around the vessels forms the haversian system, the osteon. This represents the ontogenetically and phylogenetically highest unit of bone development. The cells of this shell bone are long and slender. The delicate canaliculi may be demonstrated best by the thionin-picric acid method (Schmorl¹⁰) or with ground sections (Weber¹¹). The cells lie in regular order. The fact that connective tissue fibers (Sharpey fibers) are included in this lamellar bone under the periosteum offers no hindrance to the classification of this bone (lamellar fiber bone, Kolliker) with the shell bone of Weidenreich. This conception is based on the observation that the principle modus of the development of the so-called lamellar fiber bone (except for the fact that it contains fibers, owing merely to its location) is identical with that of the true lamellar bone of the endosteum, which normally never contains fibers.

5 *The Resorption*—Each of the foregoing processes may be interrupted at any point by processes of resorption. Most frequently, the resorption involves the highest unit, the shell bone. Thus, the resorption must be regarded as a separate stage, in which the already completed bone is carved into its ultimate form. The resorption is closely related to the blood vessel system. The blood vessels themselves may have a resorbing influence by means of their walls. For the most part, the resorption is induced by osteoclasts. They are supposed to have originated as "detached vessel buds" from the endothelial cells of the blood vessels. Each may have one or more nuclei. They represent the same tissue cells as the osteoblasts, only in a different functional rôle. In normal bone there is a definite correlation between the function of the osteoblasts and that of the osteoclasts.

10 Schmorl, G. Die pathologisch-histologischen Untersuchungsmethoden, Leipzig, F. C. W. Vogel, 1925, p. 259.

11 Weber, M. Schliffe von macerierten Rohrenknochen und ihre Bedeutung für die Unterscheidung der Syphilis und Osteomyelitis von der Osteodystrophia fibrosa sowie für die Untersuchung fraglich syphilitischer, prähistorischer Knochen, Beitr. z. path. Anat. u. z. allg. Path. **78** 441, 1927.

Disturbances in this correlation are pathologic and lead to changes in the form of the bone

The description of the system of the bone-building apparatus just given is a schematic presentation of morphologic observations. Therefore, it has its weak points just as any schema of biologic processes. The difficulties may in the future be eliminated by further investigations on the basis of the facts already gained. At present, however, as a working hypothesis, this scheme is of the greatest significance in investigations of the nature of bone diseases as yet obscure. In a recent detailed German paper,¹² I attempted to analyze the nature of osteodystrophia fibrosa (so-called ostitis fibrosa) on the basis of this schema. Thus, the nature of this disease could be explained in an entirely new manner. The observations did not contradict the older knowledge, but rather supplemented it.

Based on the typical case of osteogenesis imperfecta (reported herein), the following chapter will be devoted to the analysis of the nature of osteogenesis imperfecta.

DEVIATIONS OF THE BONE-BUILDING SYSTEM FROM THE NORMAL IN OSTEOGENESIS IMPERFECTA

The Undifferentiated Mesenchymal Tissue—Qualitative changes of this stage could not be recognized morphologically. A loose reticulated marrow with disseminated lymphoid and myeloid elements occupied the cavities of the cortex and surrounded the cartilaginous remnants situated within the marrow cavity. A great number of these splinters lay completely or almost entirely free, without surrounding reticulated marrow (fig. 6). Von Recklinghausen already has observed this lack of "germinal tissue." He found a superabundance of lymphoid marrow at the expense of bone-forming tissue. He believed it to be a "metaplasia," a transformation of bone-forming into blood-forming tissue (or marrow). Therefore, he designated osteogenesis imperfecta as "myeloplastic" malacia. While the tissue of the first stage was qualitatively normal, as to morphology, it is in its entirety quantitatively reduced.

The Differentiation and Increase of Intercellular Substance—The preliminary stage in the development of fiber bone could be demonstrated clearly in each of the bones examined. Particularly under the periosteum could differentiation of mesenchymal cells into fibrous tissue be observed in which an increase of intercellular substance appeared (fig.

¹² Weber, M. Osteodystrophia fibrosa, ihre pseudotumor- und cystenbildende, juvenile, hyperostotisch-porotische Form beim Hund, zugleich ein Beitrag zur Frage ihrer Pathogenese und Aetiologie, Beitr. z. path. Anat. u. z. allg. Path. 81: 383, 1929.

7), repeating the normal process. This preliminary stage of fiber bone formation (fibroblastic osteoid) was found also in the callus of the fractures. Here, the marrow spaces were nearly completely filled with fibrous marrow.

The cartilage tissue appeared normal (Schmidt,¹³ Dietrich,² Haibitz⁹), relative to the age of the child. In several bones, larger cartilage islands were located below the periosteum midway between the epiphyseal line and the middle of the diaphysis. In the region of the fractures, a cartilage formation occurred in a so-called "metaplastic" manner. This cartilage, however, did not originate in a truly metaplastic way, but rather originated from a proliferation of a germinal tissue ontogenetically destined to provide either cartilage or fiber bone. The stimulus for the local proliferation of cartilage is probably referable to mechanical factors.

As far as morphology was concerned, there were no special disturbances of the preliminary phase, qualitatively. In comparison with that in a normal child of the same age, this stage was also not reduced quantitatively. Nevertheless, in the region of the fractures (i.e., under abnormal conditions) an increase of this stage was evident.

The "Nucleus" Formation—The cartilage was regularly opened up (Bauer³ and others) by means of blood vessels. The intercellular substance was calcified in a normal degree. The cartilage, also, underneath the periosteum and the callus showed a normal degree of calcification. Aside from the conditions prevailing in the fractures, the cartilaginous "nucleus" formation was not increased quantitatively and was qualitatively of normal morphology.

In regard to the fibroblastic bone formation, conditions were markedly different. In comparison with a normal new-born infant, the following is stated. Normally, fiber bone is found in great abundance between the osteons of the cortex, as a so-called "rootstock" (Gegenbaur) and invariably at tendinous insertions. Imagine for a moment that these haversian systems have disappeared. A skeleton of fiber bone remains. If now, one compares this hypothetical normal framework of fiber bone with the fiber bone actually present in osteogenesis imperfecta, one notices that there is no smaller quantity of fiber bone than in the normal state. Indeed there seems to be more fiber bone in osteogenesis imperfecta than in the normal state. This may be explained in two ways. On the one hand, more fiber bone may have been formed (i.e., absolute increase) or, on the other hand, the fiber bone, though formed in normal quantity, was not sufficiently resorbed (i.e., relative increase). Probably the latter offers the more satisfactory explanation, for no

¹³ Schmidt, M. B. Der Bewegungsapparat, in Aschoff. Pathologische Anatomie, Jena, Gustav Fischer, 1928, vol. 2, p. 190.

process of resorption by osteoclasts could be observed, except in the regions of the fractures. The thickening of the bone in the callus was due to abundant fiber bone. Thus, an absolute increase of fiber bone was indicated in this region. This fiber bone, however, did not exceed a callus formation which might be observed in any callus of a normal bone.

Now the question of the quality of the fiber bone arises. It was stated that there were severe changes in the composition of the intra-cellular substance, which appeared now scaly, now granular-crumbly or with bluish-red stippling. A great number of splinters had a deep blue margin which von Recklinghausen¹ interpreted partly by "tysis". On the whole the calcification seemed to be quantitatively normal for the newly formed fiber bone stained conspicuously blue. This observation has also been made by nearly all earlier authors. There was evidently a disturbance in the composition of the intercellular substance which was of inferior quality. The cells included in the intercellular substance also showed changes, which may be related to the changes in the matrix. The cells were peculiarly round and vesicular. Their nuclei were rounded, too, and had a clearly visible chromatin network. It does not seem plausible that these changes were caused by "oncosis" of formerly normal bone cells. Rather, this was a young newly formed fiber bone which was of inferior value from the start.

The Shell Bone—Shell bone had originated only in a few layers in the neighborhood of the fractures. This lamellar bone did not appear as osteoid, but was immediately well calcified. Except for these few layers of lamellar bone, every trace of a shell bone formation was lacking in the whole skeleton (Bauer & Looser¹⁴). The entire bone picture then, exclusive of the fractures, gave the impression that the lamellar bone had been lost from the young bone of the new-born infant, and that only the framework of the rootstock, the fiber bone, had remained. An analysis of the bone picture reveals, however, that the lack of shell bone was under no circumstances referable to a direct disappearance (i. e., resorption) of shell bone formerly present, but rather to a complete lack from the beginning.

The Resorption—Processes of resorption induced by giant cells were observed only in the region of the callus, where they were considerably augmented. Nowhere else in the whole skeleton could a single osteoclast be found, nor was any particular resorption by vessels to be demonstrated.

¹⁴ Looser, E. Zur Kenntnis der Osteogenesis imperfecta congenita und tarda (sogenannte idiopathische Osteopathysen), *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **15** 161, 1906.

THE NATURE OF OSTEOGENESIS IMPERFECTA

In discussing the analysis of the bone picture, the observations concerning the fractures will be disregarded temporarily. Their immediate consideration would complicate the conclusions at this stage. Although the fractures are an integral part of the clinical picture of osteogenesis imperfecta, they have arisen only secondarily. They must be regarded as a mechanically determined logical consequence of a primary disturbance of the bone system. The bone picture of the fractures in particular can be understood only if the nature of the osteogenesis imperfecta has been determined in general.

From the analysis of the bone picture, one may draw the following conclusions as to the nature of osteogenesis imperfecta.

1 Osteogenesis imperfecta is a generalized disease of the bone-building system. The entire skeleton is involved in the same manner.

2 The disease is congenital. Its origin is traceable far back into the intra-uterine period, as may be concluded from the dense callus formation surrounding the fracture.

3 The bone picture of osteogenesis imperfecta is one of arrested development which manifests itself both in a passive and in an active aspect.

4 The passive expression of the arrested development is the lack of the highest unit, the osteon. Either there are no osteoblasts present or they cannot perform their destined function of producing shell bone.

5 This arrest is not secondary, as in osteodystrophia fibrosa, but rather primary, i. e., a formation of lamellar bone has never occurred.

6 The active aspect of the arrested development finds its expression in the bone tissue actually present. The analysis shows that the entire skeleton in osteogenesis imperfecta consists of fiber bone. As stated, this type of bone is ontogenetically and phylogenetically the oldest type of bone tissue and forms the "nucleus" for the consequent deposition of shell bone. Thus, one may conclude that the bone tissue has been arrested in the stage of "nucleus" formation. Also cartilage is present as "cartilaginous nucleus."

7 The bone picture as a whole is a representation of the combined passive and active components of the arrested development. The result of the combination in regard to the bone picture is "a relative displacement to the left." This statement may require some explanation. The term "displacement to the left" is well known in connection with diseases of the blood-building system. If one should graphically present the quantity of the single stages of the bone-building system in osteogenesis imperfecta beginning from the left, the following would result. The highest stage of the development, on the extreme right, would be

completely lacking. The middle stages would be seemingly greatly increased whereas they are in truth only relatively increased, i. e., the fiber bone is formed in normal quantity, but not resorbed by osteoclasts, which are lacking completely. The youngest stage would, in fact, be decreased absolutely.

8. The fiber bone forming the skeleton in osteogenesis imperfecta shows pathologic changes of its intercellular substance. One is dealing with a fiber bone of inferior quality. Since this pathologic fiber bone has arisen from an embryonal tissue of fetal origin one may well speak of a congenital faculty differentiation or malformation.

Summarizing: Osteogenesis imperfecta is a congenital primary generalized arrested malformation of the bone-building system with a "relative displacement to the left" of the bone picture.

In this connection, one may consider the relation to several other bone diseases. I have designated the nature of another of the 'malacic' bone diseases, osteodystrophia fibrosa, as "imitation of the bone-building system with consequent (absolute) displacement to the left of the bone picture." Here, too, one observes malformations which, however, originate from a differentiation of a newly arisen mesenchyme. This disease involves a formerly normal skeleton, and thus presents a secondary dystrophy, which may also appear in a localized form. In fact, in those places in osteogenesis imperfecta in which the arrest of differentiation has been replaced by a stimulation, the picture is identical with one of an osteodystrophia fibrosa. Such conditions are found in the regions of the fractures. Here all the requirements are met which von Recklinghausen postulated for the diagnosis of a typical "ostitis fibrosa": fibrous marrow, giant cells, fibroblastic osteoid and fiber bone formation. Cysts, also, were observed, and malformed fiber bone as actually observed in the pseudotumors or brown tumors in osteodystrophia fibrosa. By the stimulation of the bone-building apparatus in these areas, a minimal formation of shell bone has occurred in a manner like that observed in osteodystrophia fibrosa.

Another disease that is frequently mentioned in connection with osteogenesis imperfecta is otosclerosis. In a recent paper,¹⁵ I designated otosclerosis as a localized osteodystrophia fibrosa. It is my intention to present in the near future the pathologic changes of the petrous bone in the present case and to investigate its relation to otosclerosis.

The relation of osteogenesis imperfecta to Moeller-Bailow's disease requires a brief consideration. Juvenile scurvy is characterized by the fact that shell bone apposition ceases, while normal resorption continues. This arrest of shell bone formation attacks an originally

15 Weber, M. Otosclerosis in Its Histogenic Relations to Osteodystrophia Fibrosa (Ostitis Fibrosa), *Arch. Otolaryng.* **11** 1 (Jan.) 1930.

normal skeleton. Further investigations seem desirable in order to clarify the conditions as to the fiber bone. Besides, a hemorrhagic diathesis leading to hemorrhages is typical of scurvy. In my case, hemorrhages could not be observed within the organs, but were observed underneath the periosteum and within the bone-marrow. Presumably, the hemorrhages in osteogenesis imperfecta may be due to mechanical disintegration. From this it may be, perhaps, concluded, with all conservatism, that there are genetic relations between osteogenesis imperfecta and Moeller-Barlow's disease. Further research must clarify this question.

CONCLUSIONS CONCERNING THE CAUSE AND THERAPY

From the knowledge of the nature of osteogenesis imperfecta acquired from the analysis of its bone picture, one may make certain conclusions concerning the cause and therapy.

The etiology of osteogenesis imperfecta is still unknown. The question arises "Is there a germinal (*vitium primae formationis*) or a secondary disturbance?" In order to clarify this question it seems advisable to investigate at first where the functional point of attack might be situated which could explain a germinal as well as a secondary disturbance.

In osteogenesis imperfecta, either the osteoblasts, as well as the giant cells, are lacking or they do not carry on their destined function. Both types of cells originate from the endothelial cells of the blood vessels. Thus, the endothelial cells in general may be held responsible for the changes in the bone picture. Severe arteriosclerotic changes observed by many authors in young children with osteogenesis imperfecta point likewise to an involvement of the walls of blood vessels.

This juvenile arteriosclerosis in cases of osteogenesis imperfecta indicates also a disturbance in the composition of the intercellular substance in the same sense as the pathologic fiber bone formation in osteogenesis imperfecta might indicate such a disturbance. Thus, one may conclude that the changes are traceable as far back as the mesenchyme (Bauer³).

Attempts have been made to solve the question as to whether one is dealing with a primary or a secondary disturbance of mesenchyme by examination of the teeth. It is plausible that the oldest hard substance of the body, the teeth, in osteogenesis imperfecta might be normal in their original anlage. Indeed, Biebl¹⁶ stated that the primary layers of dentine observed in a case of osteogenesis imperfecta were normal. The teeth in my case will be examined by Dr. Heimann Becks, and the report will be published in the *Journal of the American Dental Asso-*

16 Biebl, M. Beitrag zur Frage der Osteogenesis imperfecta durch Untersuchungen am Zahnsystem, *Virchows Arch f. path. Anat.* **255** 54, 1925.

ciation Dr Becks has accorded me the privilege of giving out the following statement concerning the teeth "The dentine in the case under discussion shows severe changes There is, however, no indication that the dentine first deposited was ever normal" Thus, we cannot confirm Biebl in regard to this case and rather would like to agree with Bauer³ and Kaufmann,⁴ who believed that there is a *vitium primae formationis* But in spite of the observations, it might be possible that one is dealing with a secondary process, for, in the bone and in the tooth system identical histologic changes might be caused by a disturbance of the anlage or by an early secondary disturbance of the mesenchyme which persists On the other hand, however there is the improbable possibility that two types of osteogenesis imperfecta exist The one would be a *vitium primae formationis* and the other a dystrophy, beginning early An elucidation of this question could hardly be established by morphologic studies, but must be approached rather by experiments on pregnant animals A diet (perhaps a modified scurvy diet) resulting in an arrested malformation of bone producing a displacement to the left of the bone picture may possibly produce an osteogenesis imperfecta in the offspring

Also, in regard to therapy, one may develop some fundamental thoughts The attempt must be made to overcome the arrest in development of the bone-building system which has its functional location in the walls of the blood vessels and the composition of the intercellular substance The formation of the shell bone must be stimulated Then, the loose framework of the cortex, consisting of fiber bone, would be filled with lamellar bone How this might be accomplished no one exactly knows Systematic investigations as to the influence of diets and other factors on the single phases of the bone-building system will have to clear these questions

SUMMARY

The pathogenesis of osteogenesis imperfecta is examined from a new standpoint The investigations are based, on the one hand on a case of osteogenesis imperfecta observed in a 2 day old guinea pig and on the other hand, on the newer knowledge gathered from the international literature The normal bone-building system, described previously by the author is used as a foundation for the analysis of the observations This system presents the single time phases of the normal development of bone, the combination of which is designated as the "bone picture" The deviation of the single phases from the normal constitutes the bone picture in osteogenesis imperfecta It is demonstrated that the youngest stage in the case reported was qualitatively of normal morphology and quantitatively reduced The highest stage, the lamellar bone or shell bone, was completely lacking, as was also the process of resorption by

osteoclasts. The conclusion is drawn that in osteogenesis imperfecta the entire bone system has been arrested in the stage of "nucleus formation," i. e. the bone actually present consists of fiber bone which, forming the foundation of lamellar bone, must be sharply differentiated morphologically from the latter. This fiber bone is of inferior quality and shows a relative increase in quantity. The cartilage is evidently normal and opened up in a normal way. Thus, osteogenesis imperfecta must be regarded as a congenital primary generalized arrested malformation of the bone-building system which leads to a "relative displacement to the left" of the bone picture. Presumably, the disease is traceable as far back as the endothelial cells of the blood vessels and the composition of the intercellular substance. Whether a *vitium primae formationis* or a secondary disturbance must be held responsible could not be determined in this case. The fractures are only a local secondary mechanical result of the primary disturbance of the bone system in general. They reveal the picture of osteodystrophia fibrosa, which the author has designated previously as "irritation of the bone-building system leading to an absolute displacement to the left of the bone picture." Finally, certain new points of view as to etiology and therapy are briefly discussed and methods suggested for the solution of questions still open.

ADENOFIBROSARCOMA OF THE BREAST^{*}

LAWRENCE H. SOPHIAN, M.D.

NEW YORK

Sarcoma of the breast is in contrast with carcinoma of the breast in that while the latter forms about the best understood group of neoplasms, the former remains poorly classified, and the relation between pathologic type and clinical course is still obscure.

The confusion in the group of sarcoma of the breast has arisen from ill adapted criteria for its subdivision and the inclusion of all malignant tumors not definitely epithelial. On more painstaking examination, some of these tumors made up of large spindle-shaped cells loosely connected and without definite stroma have shown scattered foci of well-defined medullary epithelial structure (Ewing¹). It is probable that most of the tumors described as carcinosarcoma and many of the round and spindle-cell alveolar sarcomas are really atypical carcinomas.

It is conceivable that in the connective tissue of the breast any tumor of mesenchymal origin may arise, as well as mixed tumors and teratomas. Such cases have been reported. Chondrosarcoma and mixtures of chondromatous and epithelial elements appear to be only moderately rare. In carcinoma, the stroma may undergo metaplasia and the occurrence of cartilage and bone in it has been reported.

One type of sarcoma appears to be specific for the breast, this is one in which an admixture of epithelium-lined spaces is found. In its earliest stage this type of tumor is identical with adenofibroma, except for a more active proliferation of the fibroblastic tissue. The relative importance of the epithelium and of the fibrous tissue in adenofibroma remains in some dispute. Certain authors (Virchow²) believe that the proliferation is primarily of the connective tissue, while others (Schimmelbusch³) consider that the fundamental and primary change is in the epithelium. At puberty and in pregnancy there is an active proliferation of acini accompanied by a proliferation of the pericanalicular and periacinous connective tissue, and such changes, localized and accentuated, perhaps in a superfluous or misplaced lobule, give rise to a

^{*} Submitted for publication, Nov. 7, 1929.

^{*}From the Pathological Laboratories, Palmer Memorial and Collis P. Huntington Memorial Hospitals, Boston.

1 Ewing, James. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 540.

2 Virchow, R. L. *Die Krankhaften Geschwulste*, 1863, vol. 1, p. 328.

3 Schimmelbusch, in Langenbeck. *Arch. f. Chir.* **44**: 102, 1892.

mixed tumor, adenofibroma (Cheate⁴) It would seem that there is a fairly even balance between the proliferation of the connective tissue and of the epithelium Cases of pure fibroma of the breast (Williams⁵) and of pure adenoma of the breast (Cheate⁴) are reported, but are extremely rare compared with the cases of mixed tumor

Eventually, either the epithelial or the fibrous element may predominate in an adenofibroma, and from such overgrowth either carcinoma or fibrosarcoma may develop I have observed several cases in which the histologic features of adenofibroma were well preserved, and in one portion the epithelium appeared in actively proliferating strands invading the stroma Fibrosarcoma arising in adenofibroma is a definite type of sarcoma of the breast, recognizable by gross and histologic features, and apparently running a clinical course different from other sarcomas of the breast Fifteen cases of this have been collected from the material of the laboratory of the Huntington Hospital and from that of the Palmer Memorial Hospital, accumulating during the last ten years at the former hospital, and during the last two years at the latter

The fifteen cases are tabulated in the appended chart It will be seen that seven cases 1, 4, 6, 11, 13, 14 and 15, were found to present features that enabled me to make the histologic diagnosis of adenofibrosarcoma This proportion cannot be considered significant because the number of cases is small, but it is noteworthy that Ewing¹ stated that true adenosarcoma of the breast is rare On the other hand, Deaver and MacFarland⁶ in their compilation of cases of sarcoma of the breast gave a total of 193 cases of adenosarcoma occurring in a group of 838 sarcomas of the breast In the series reported by Gross,⁷ 33 per cent of a total of 156 cases of sarcoma of the breast are termed "adenoid," and may be presumed to belong to the category of adenosarcoma Finsterer⁸ reported forty cases, eighteen of which he considered as "cystosarcoma" This group, too, may correspond to the special variety of sarcoma under discussion

The relative frequency of this type of tumor is of about the same magnitude in my series as in the aforementioned series reported by others

It is, perhaps, noteworthy that the only two cases of sarcoma of the breast in the records of the Palmer Memorial Hospital are both cases

4 Cheate, S L Mastitis, Cysto-Adenoma and Adenoma of Breast, Arch Surg **17** 535 (Oct) 1928

5 Williams, R M Chron **19** 289, 1894

6 Deaver and MacFarland The Breast, Philadelphia, P Blakiston's Son & Company, 1917, p 372

7 Gross, S W Sarcoma of Female Breast, Am J M Sc **94** 17, 1887

8 Finsterer J Ueber das Sarkom der weiblichen Brustdruse Deutsche Ztschr f Chir **86** 352, 1907

of adenofibrosarcoma I consider this to be in accordance with the development of these tumors in that a high proportion of neoplasms seen at this hospital are in the early stages. These cases would, in my view, represent examples of early sarcoma of the breast at a stage in which the remains of the original mixed structure can be recognized.

Of the group of fifteen patients, the youngest was 29 years old and the oldest 75. The ages of the seven with adenofibrosarcoma ranged from 29 to 65. The age incidence does not seem to have special significance, apart from the fact that a benign adenofibroma of long standing may become sarcomatous, and this interval brings the patient into the region of middle age. In the total group, the duration of disease as given by the patient's history varied from three weeks to twenty years. In the included special group, the variation was also wide, so that no deductions from this factor seem possible.

All the tumors were of considerable size, even those the duration of which was reported as only three weeks. The smallest was said to be as large as a walnut, and the largest the size of a football. In the seven cases of adenofibrosarcoma, the tumors were of more nearly uniform size, ranging from the size of a goose egg to that of a football, with the intermediate ones fairly similar in magnitude. The fact that these tumors were all of considerable size seems of importance in two respects, first, in indicating a fairly long duration, probably more nearly uniformly long than was shown in the histories, and second, in furnishing a feature distinguishing adenofibrosarcoma from adenofibroma, which is usually not more than 5 or 6 cm. in diameter, and is most commonly reported clinically to be the size of a walnut.

Histologically, these cases have been divided into two groups, one with, and the other without, epithelial elements. All show more or less active fibroblastic tissue, with closely packed spindle-shaped cells, showing at least a few mitoses. In the group with epithelial elements, the arrangement is that seen in adenofibroma. There are clefts and ducts lined with cuboidal, columnar or stratified epithelium. The lumen is often more or less compressed and frequently contains desquamated epithelial cells. The fibroblasts are usually most closely packed immediately about the ducts, and in these regions most of the mitoses are to be noted. Farthest from the ducts, the fibrous tissue may be fairly acellular and the collagen dense and even hyaline. This patchy appearance, with active proliferation about the ducts and relative quiescence between them, is a fairly constant feature of these tumors early in their development. In one case, the intercellular substance was distinctly myxomatous (case 14). In another (case 6) there were only a few epithelium-lined spaces and between them was a uniformly cellular fibroblastic tissue, in which mitoses were numerous. This seemed histo-

logically a form intermediate between pure fibrosarcoma and adeno-fibrosarcoma, and clinically behaved more like the former than the latter



Fig 1—Gross specimen in case 14, natural size. Only on the upper aspect is the encapsulation well defined.

A comparison of the histology and the clinical course tends to emphasize a difference between the two groups. In four of eight cases histologically fibrosarcoma, the subsequent course is unknown. In

three of the remaining four cases, the patients died of recurrence or metastases within eight months of operation. In one case of fibrosarcoma histologically of low malignancy, the patient remained well and was apparently free from recurrence six years after operation.

In the group diagnosed as adenofibrosarcoma there were seven cases. In five of these the patients were free of disease when last heard from, that is, from six months to seven years after the removal of the tumor. One (in case 1) had a recurrence four and one-half years after operation. This recurrent tumor was histologically considered to be fibrosarcoma, with no remaining trace of the original mixed structure. This observation, that a recurrence of an adenosarcoma may be a pure spindle cell sarcoma, was made by Finsterer.⁸ The last case (no. 6) was intermediate in type histologically, and two recurrences appeared at intervals of six months and two months. Death occurred a year after operation. At this time, an abdominal tumor was said to be present, suggesting the possibility of metastasis.

The comparison in the clinical courses of cases of fibrosarcoma and adenofibrosarcoma may be made from the following cases.

M. C. (case 10), a housewife, aged 43, having seven children, came to the Huntington Hospital, April 1, 1924, because of swelling of the left breast. This had first been noted ten months previously as a lump the size of a hickory-nut, and growth had been constant. On examination, the left breast was found three times the size of the right. The skin was tense and marbled and seemed about to ulcerate. Axillary nodes were clinically negative. The tumor was movable, lobulated and elastic.

April 7, 1924. An amputation of the breast was performed by Dr. Robert Greenough. The axilla was not disturbed. In gross, the mass measured 7 inches (17.78 cm.) in diameter, and showed necrotic and cystic foci.

April 21, 1924. A small recurrence was noted in the granulating wound. Nine seeds each containing 1 millicurie of radium emanation were applied. May 8, 1924, the patient was discharged with two definite recurrences in the operative wound.

Microscopic study showed a pure fibrosarcoma, with large atypical spindle cells showing numerous mitoses, and a varying amount of intercellular substance. The patient died, Aug. 11, 1924, clinically with metastases, four months after operation. Permission for postmortem examination was not obtained.

M. R. P. (case 13), a widow, aged 48, with one child, noticed a lump in the left breast, associated with stabbing pain, three weeks before coming to the Palmer Memorial Hospital. On examination, Sept. 27, 1927, the left breast was found twice the size of the right. In it was a hard, movable mass. The axillary glands were clinically negative.

Sept. 29, 1927. Radical mastectomy was done by Dr. L. S. McKittrick. In gross there was seen a well outlined tumor as big as a man's fist. This was histologically found to be made up of bundles of cellular fibroblastic tissue, with numerous mitoses scattered in the cells. Between the bundles were clefts and tubules lined by columnar and squamous epithelium. Healing was uneventful, and examination at subsequent visits showed a smooth scar, without evidence of recurrence.

It is to be noted that in neither of these cases was there any involvement of the axillary lymph nodes, nor was it reported as having been observed in any of the other cases of sarcoma of the breast. It would seem that there is no reason, therefore, for using the more difficult operation in cases of sarcoma. Finstere⁸ also found no metastases

Summary of Cases of Sarcoma of Breast

Case	Age	Duration	Size	Histologic Character	Clinical Course
1	61	2 years	"Football"	First specimen, adenofibrosarcoma, second, pure fibrosarcoma	Recurrence 4 years after removal of first tumor
2				Infiltrating bundles of spindle cells, with numerous mitoses, fibrosarcoma	Unknown
3	47	2 years		Infiltrating bundles of spindle cells, with numerous mitoses, fibrosarcoma	Unknown
4	65			Cellular fibroblastic tissue in which were spaces lined by epithelium, adenofibrosarcoma	Well and healed
5	60	5 months	"Egg"	Spindle cells and giant cells, with many mitoses, fibrosarcoma	Unknown
6	48	5 months	"Goose Egg"	A few epithelium lined spaces, in very cellular fibroblastic tissue with mitoses	Recurrence twice and death 1 year later
7	40	9 years	5 in, diameter	Spindle cells, with abundant collagen and few mitoses, fibrosarcoma	Well and healed
8	53	5 months	10 in, diameter	Spindle cells, with many mitoses and little collagen, fibrosarcoma	Metastases, died 8 months later
9	59	6 weeks	"Walnut"	Infiltrating cellular fibroblastic bundles, many mitoses, fibrosarcoma	Died 6 months after operation
10	43	1 year	17 cm, diameter	Closely packed spindle cells, with mitoses, fibrosarcoma	Recurrence and death in 4 months
11	29	5 months		Numerous epithelium lined clefts, cellular fibrous tissue with many mitoses	Well and healed
12	75	3 weeks		Spindle cells and giant cells with mitoses	Unknown
13	48	3 weeks	"Fist"	Epithelium lined clefts with cellular fibrous tissue showing mitoses, adenofibrosarcoma	Well and healed
14	51	6 months	"Orange"	Same as in case 13, with myxomatous fibrous tissue, adenofibrosarcoma	Well and healed
15	51	20 years	"Child's head"	Epithelium lined clefts with fibrous tissue showing foci of condensation, with mitoses, adenofibrosarcoma	Well and healed

to lymph nodes in his series of forty cases. His statistics are also of interest as regards prognosis in the presence of various types of sarcoma. He classified eighteen of forty cases as "cystosarcoma," a term which appears suggestive of the group I have separated as cases of adenofibrosarcoma. He found twelve of the patients in these eighteen cases free of disease, one with a recurrence, five dead of intercurrent

disease and none with metastases, when they were reexamined over periods of several years after operation. These cases contrast with the ones he classified as cases of round and spindle cell sarcoma, in

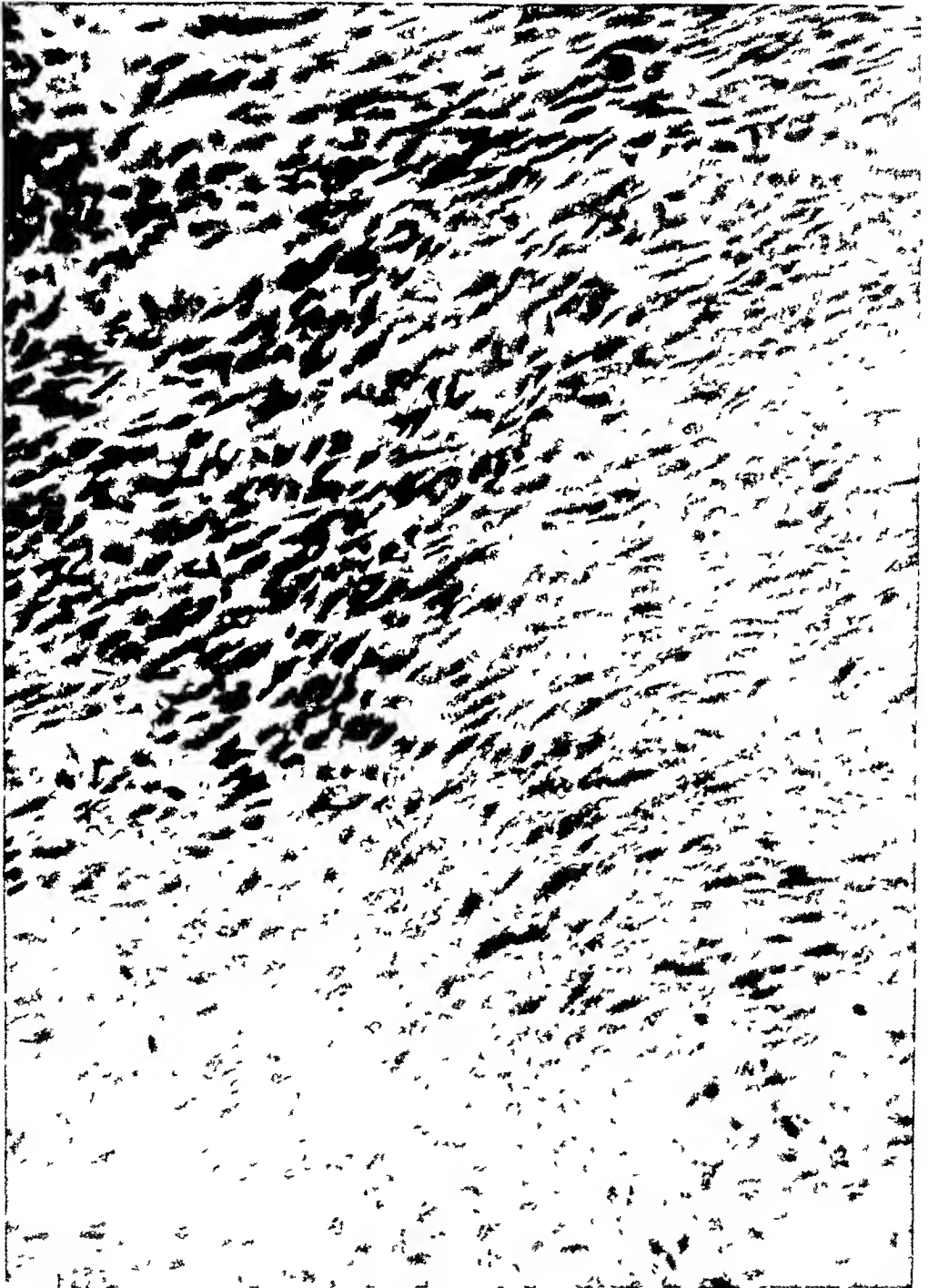


Fig 2—Actively proliferating focus in section from case 13, $\times 300$. Several mitotic figures may be distinguished in the paler portion of the field.

which only five of the twenty-one patients were free from disease, nine showed recurrences, three showed metastases and the condition of the rest were unknown.

From this series of cases, it appears that there is a definite difference in malignancy between fibrosarcoma and adenofibrosarcoma, apart from the ordinary criteria of cell activity in the fibroblasts themselves, and that the latter is considerably less malignant than the former. Two explanations appear possible. First, it may be that all sarcoma of the breast begins as adenofibroma and passes through an intermediary stage of adenofibrosarcoma. In this case, fibrosarcoma would be a more malignant tumor because of its longer standing and more advanced condition. The second possibility is that there exists a growth-restraining influence, perhaps, mutual, between the epithelial and connective tissues, and that this is sufficient to make the mixed tumor a less malignant one. The fact that an intermediate form of tumor occurred in this series is in favor of the former explanation. It has long been observed clinically that small tumors of the breast, such as are found on removal to be adenofibroma, if left undisturbed, may after months or years begin to grow and reach enormous size. Such tumors form the large ulcerated, fungating sarcomas of the breast occasionally seen. The fact that recurrences of adenosarcoma are known to appear as fibrosarcoma is further evidence that this graduation from benign to more and more malignant forms takes place.

I should consider the presence of epithelial elements in a sarcoma of the breast as significant in indicating an early stage of malignancy. It seems probable that if such tumors were allowed to grow uninterruptedly, the fibroblastic element would finally completely displace the epithelium. Consequently, it seems that the preservation of the basement membrane of the epithelium is just as much an indication in sarcoma that the fibroblasts have not yet grown beyond bounds, as it is in chronic mastitis that the epithelial hyperplasia has not become carcinoma.

CONCLUSIONS

In the heterogeneous group of sarcomas of the breast, the adenofibrosarcoma is a distinct type. Adenofibrosarcoma is a comparatively frequent variety of sarcoma of the breast. It is probable that adenofibrosarcoma arises from a preexisting adenofibroma, and that it may progress to or appear in recurrences as pure fibrosarcoma. The prognosis in cases of adenofibrosarcoma is fairly good, and seems considerably better than in cases of pure fibrosarcoma.

THE THYMUS GLAND IN LYMPHATIC LEUKEMIA

ITS BEARING ON THE HISTOGENESIS OF THE SMALL THYMIC CELLS *

HARRY M MARGOLIS, MD
Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN

Since Kolliker,¹ in 1879, drew attention to the epithelial anlage of the thymus gland in the branchial clefts, there has been considerable study in an attempt to determine the definite histogenetic nature of the organ. Yet many facts regarding the histogenesis of the thymus gland are still the subject of dispute, and this despite many excellent contributions that have been made on this subject.

In the course of an investigation of the thymus gland under certain pathologic conditions, I became particularly interested in the histogenesis of that component of the thymic parenchyma variously described as the "small thymic cells" or the "thymic lymphocytes." The histogenetic relationship of these cells to the original epithelial anlage has been the crux of a controversy which has attracted considerable comment, but which is, nevertheless, still settled.

HYPOTHETICAL SOURCES OF SMALL THYMIC CELLS

It may be said that two theories are at present most commonly held with reference to the source of the small thymic cells. According to one of the two theories, these cells are considered of mesodermal origin whereas, according to the other, they are derivatives of the original epithelial anlage of the branchial entoderm. The studies of Maximow,² Pinner,³ Danachakoff,⁴ and Pappenheimer⁵ all have tended

* Submitted for publication, Nov 22, 1929

* Work done in the Section on Pathologic Anatomy, the Mayo Clinic

1 Kolliker, Albert. *Entwicklungsgeschichte des Menschen und der höheren Thiere*, Leipzig, Wilhelm Engelmann, 1879, pp 875-882

2 Maximow, Alexander. *Untersuchungen über Blut und Bindegewebe*. II. Ueber die Histogenese der Thymus bei Säugetieren, *Arch f mikr Anat* **74** 525, 1909, IV. Ueber die Histogenese der Thymus bei Amphibien, *ibid*, **79** 560, 1912, V. Ueber die embryonale Entwicklung der Thymus bei Selachiern, *ibid* **80** 39, 1912

3 Pinner, Max. Zur Frage der kleinen Thymusrindenzellen. Frankfurt Ztschr f Path **23** 479, 1920

4 Danachakoff, Vera. The Differentiation of Cells as a Criterion for Cell Identification, Considered in Relation to the Small Cortical Cells of the Thymus, *J Exper Med* **24** 87, 1916

5 Pappenheimer, A M. Further Studies of the Histology of the Thymus, *Am J Anat* **14** 299, 1913

to indicate the morphologic identity of the small thymic cells with the blood lymphocytes. However this does not imply histogenetic unity of the thymic cells and the true blood lymphocytes. Indeed, as has already been pointed out by Danchakoff, studies by the method of tissue culture have indicated that the form of the cell can be influenced considerably by various environmental factors. Hence, cellular morphology and even cellular differentiation, which is only a further expression of a potentiality for morphologic variation, cannot be adduced as final proof of biologic or histogenetic identity among cells. Somewhat more direct studies to determine the origin of the small thymic cells have been made by Rudberg⁶ and Johnson,⁷ who have studied the regenerative process in the thymus gland following experimental involution. These investigators concluded that the reappearance of the "lymphocytes" following involution was dependent on the immigration of lymphocytes into the epithelial network. However these conclusions seemed untenable to Gottesman and Jaffe,⁸ who studied the regeneration of autoplasmic thymic transplants in albino rats. They were unable to demonstrate any evidence of lymphocytic infiltration from without and felt that the small thymic cells arose in situ from the proliferation of the reticular epithelium. Many more detailed histologic studies of the thymus gland in young embryos of the human being and of lower animals have indicated the epithelial origin of these thymic cells. The extensive studies of Stohr,⁹ Prenant,¹⁰ Nusbaum and Prymak,¹¹ and those of Bell,¹² all have shown rather strikingly that following the transformation of the solid epithelial organ into the reticular network, there appeared the small thymic cell by a process of budding from the reticular epithelial cells. The gradual transition between the epithelial cells of the reticulum and the small thymic cells was demonstrated and the definitive thymic cell then was found to break loose from the syncytium passing into the spaces of the latter and assuming its position as a part of the thymic parenchyma.

6 Rudberg, H. Studien über die Thymusinvolution. I. Die Involution nach Röntgenbestrahlung, *Arch f Anat Entwicklungsmech d Organ*, 1907 supp pp 123-124.

7 Johnson, Arvid. Studien über die Thymusinvolution. Die akzidentelle Involution bei Hunger, *Arch f mikr Anat* **73** 390, 1909.

8 Gottesman, Jessie M., and Jaffe, H. L. Studies on the Histogenesis of Autoplasmic Thymus Transplantations, *J Exper Med* **43** 403, 1926.

9 Stohr, P. Ueber die Natur der Thymus-Elemente, *Anat Hefte* **31** 407, 1906.

10 Prenant, quoted by Bell.

11 Nusbaum, Josef and Prymak, Theodor. Zur Entwicklungsgeschichte der lymphoiden Elemente der Thymus bei den Knochenfischen. *Anat Anz* **19** 6 1901.

12 Bell, E. T. The Development of the Thymus, *Am J Anat* **5** 29, 1906.

This brief review indicates the salient facts on which are based the two diametrically opposed theories now held most commonly with reference to the histogenesis of the small thymic cells. A detailed review of this subject is given by Pappenheimer¹³ and by Bell.

OBSERVATIONS OF THYMUS GLAND IN LEUKEMIA

An indirect manner of approaching the study of this problem is to investigate the reactions of the thymus gland, and particularly of the small thymic cells, under pathologic conditions in which the predominant influence is exerted on the true lymphocytic elements in the lymph nodes, blood and so forth. Thus, a study of the reactions of the thymus gland in lymphatic and aleukemic leukemia seemed to us of importance in its possibility of throwing some light on the relationship of the thymic cells to the lymphocytic elements elsewhere in the body. On a priori grounds, it may be assumed that if the small thymic cells are true lymphocytes, having not only a morphologic resemblance to blood lymphocytes, but also a common histogenetic relationship to them, there would occur in lymphatic leukemia hyperplasia of the thymus gland step by step with hyperplasia of the lymphatic structures elsewhere in the body.

A review of the literature does not reveal any extensive study from this standpoint. The recorded cases in which thymic hyperplasia was observed in patients with leukemia have yielded contradictory results, apparently owing to the limited material which was available for study. The conclusions which have been drawn from these studies parallel the contradictory evidence on which they were based.

Thorpe¹⁴ reported "an unusual case of thymic hypertrophy" in a boy, aged 7, who was suffering from lymphatic leukemia. The thymic enlargement, in this instance, was detected by means of a roentgenogram, and postmortem confirmation was not available. General examination revealed also marked enlargement of the liver and spleen, and there was significant enlargement of the lymph nodes. This author quoted De Sautelle and Wood,¹⁵ who reported similar enlargement of the thymus gland in a case of lymphatic leukemia.

Poensgen¹⁶ found a thymus gland weighing 60 Gm. in a boy, aged 16, with lymphatic leukemia, in another case, that of a man, aged 60, the thymus gland weighed 2 Gm. and histologically presented lymphocytic infiltration. From this he concluded that the thymus gland, participating in the lymphocytic reaction, must be a lymphoid organ.

13 Pappenheimer, A. M. A Contribution to the Normal and Pathological Histology of the Thymus Gland, *J. M. Research* **22** 1, 1910.

14 Thorpe, E. S. An Unusual Case of Thymic Hypertrophy, *Arch. Pediat.* **44** 126, 1927.

15 De Sautelle, W. T., and Wood, R. B., quoted by Thorpe (footnote 14).

16 Poensgen, Fritz. Beitrag zur Frage der Wechselbeziehungen zwischen Thymus, Schilddrüse und lymphatischem System, *Med. Klin.*, **2** 1504, 1913.

Hart¹⁷ was unable to report on any cases of lymphatic leukemia in children, but he had observed marked enlargement of the thymus gland in pseudoleukemia and felt that this was due to the participation of the lymphoid components of the thymus gland in the generalized lymphoid hyperplasia

Ordway and Gorham,¹⁸ in a consideration of lymphatic leukemia, stated "The thymus gland is usually large and may even show tumor-like nodules and infiltration of the surrounding tissue. Histologically, the change is comparable to that found in the lymph glands"

Kaufmann¹⁹ stated "In leukemia, marked enlargement of the thymus gland is occasionally seen, especially in acute lymphatic leukemia"

Ewing,²⁰ on the other hand, remarked "It is a notable fact that in most cases of leukemia and pseudoleukemia the thymus gland fails to participate in the process" Schridde expressed essentially the same opinion. Schridde²¹ expressed the belief that it has not been established in the literature that true thymic hyperplasia occurs in lymphatic leukemia. He was not able to observe more infiltration in the thymus gland than he observed in the skin, for example

In view of the contradictory views expressed with regard to the occurrence of thymic hyperplasia in lymphatic leukemia, I undertook a study of this problem in a series of cases of lymphatic and aleukemic leukemia which had come to necropsy at the Mayo Clinic

Between 1910 and 1929 there were thirty-two cases of acute and chronic lymphatic leukemia and aleukemic leukemia in which complete postmortem examinations were performed. In each case, the clinical and anatomic data established the diagnosis. The age of the patients varied from 2 to 73 years, ten of the cases were in children. The duration of the symptoms also varied within wide limits. On thorough analysis, it seemed desirable to classify the cases into two arbitrary groups, one in which there was no enlargement of the thymus gland and another in which there was apparent enlargement of the gland

Leukemia Without Enlargement of the Thymus Gland—Group 1 (table 1) comprised a series of twenty-eight patients, twelve of whom were aged less than 30 years. Seven of these patients were children. The ages in the entire group varied from 2 years to 73 years and the duration of symptoms ranged from five days to three years. All but seven of these patients presented, in addition to the other anatomic evidence of lymphatic leukemia, a blood picture characteristic of the

17 Hart Carl. Thymusstudien. III. Die Pathologie der Thymus, Virchows Arch f path Anat **214** 1, 1913

18 Ordway, Thomas, and Gorham, L. W. Leukemia, in Oxford Medicine, New York, Oxford University Press, 1920, vol. 2, pp. 716-718

19 Kaufmann, Edward. Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1, p. 501

20 Ewing, James, Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, pp. 967-977

21 Schridde, H. Thymus, in Aschoff, Ludwig. Pathologische Anatomie, Jena, Johann Ambrosius Barth, 1921, pp. 176-189

disease. In the other cases there was not an absolute increase in the number of circulating leukocytes, but a marked preponderance of lymphocytes, many of which were of the embryonal, immature type seen in this disease. The latter type was designated aleukemic leukemia,

TABLE 1—Cases in Which the Thymus Gland Was Not Enlarged (Group 1)

Case	Diagnosis	Age, Years	Sex	Duration of Symptoms, Mo	Leukocytes	Lymphocytes, per Cent	Pathologic Changes Noted in Thymus Gland
1	Aleukemic leukemia	2	M	2	5,700	97	Marked degree of involution, weight 12 Gm
2	Aleukemic leukemia	4	M	5	9,500	98	Marked degree of involution with fibrosis, weight 12 Gm
3	Acute lymphatic leukemia	4	M	2 25	42,600* 54,800*	99	None
4	Acute lymphatic leukemia	6	F	5 days		90	Involution and infiltration of interstitial tissue with lymphocytes, weight 3 Gm
5	Aleukemic leukemia	8	M	1	3,400	97	None
6	Aleukemic leukemia	8	M	2	3,500	71	Involution and infiltration of interstitial tissue with lymphocytes, weight 12 Gm
7	Aleukemic leukemia	9	M	2	5,200	89	Involution and infiltration of interstitial tissue with lymphocytes, weight 10 Gm
8	Acute lymphatic leukemia	19	M	4	3,800		None
9	Acute lymphatic leukemia	24	M	1 5	61,360 97,200	76	None
10	Acute lymphatic leukemia	27	M	6	23,200 364,000	99	None
11	Subacute lymphatic leukemia	25	M	9	63,400 161,000	90	None
12	Acute lymphatic leukemia	30	M	3 5 weeks	239,000 165,000		None
13	Acute lymphatic leukemia	39	F	1 5	29,500	76	None
14	Acute lymphatic leukemia	39	M	5	37,700	99	None
15	Aleukemic leukemia	40	M	3	10,000	85	None
16	Aleukemic leukemia	40	M	12	10,400	57	None
17	Acute lymphatic leukemia	42	M	1 75	110,000	79	None
18	Chronic lymphatic leukemia	45	M	24	360,000	93	None
19	Acute lymphatic leukemia	46	M	1 5	25,800	96	None
20	Chronic lymphatic leukemia	50	M	24	385,000	97	None
21	Chronic lymphatic leukemia	54	M	12	171,000 293,000	98	Marked degree of involution with infiltration of fatty areolar tissue by lymphocytes
22	Acute lymphatic leukemia	55	M	1	35,000		None
23	Chronic lymphatic leukemia	59	M	18	183,000	97	Complete involution
24	Chronic lymphatic leukemia	61	F	8	902,000	91	Practically complete involution with infiltration of fat by lymphocytes
25	Chronic lymphatic leukemia	63	M	36	313,000	94	Complete involution
26	Chronic lymphatic leukemia	63	M	15	174,000	96	None
27	Lymphatic leukemia	73	M	?		99	None
28	Acute lymphatic leukemia	73	M	?	232,000	90	Complete involution

* Lowest and highest count

since it presented all the characteristics of true leukemia, except for the absence of an increased number of circulating lymphocytes. In all instances there was found, grossly, hyperplasia of the lymphoid elements in the lymph nodes and spleen and in many cases lymphocytic collections scattered throughout the liver and kidneys.

The thymus gland was not found to be enlarged in any of these cases. In five cases, thymic tissue could not be seen grossly within

the thymic fat. Microscopic sections of the latter revealed only small collections of lymphocytes within a loose, fatty areolar tissue. The epithelial reticulum had practically entirely disappeared, and corpuscles of Hassall could not be found. In five other cases, the thymus gland was markedly reduced in size, the weights ranged from 3 to 12 Gm. Histologically, these glands presented the appearance of advanced involution. The boundary between cortex and medulla had disappeared, and the entire gland appeared much less cellular than is usual. The cortex, particularly, showed a dearth of small thymic cells. So marked was this decrease in the number of the small thymic cells that in some glands the reticulum became prominent, giving the gland more of an



Fig 1—Section of thymus gland of a child aged 4, who died from lymphatic leukemia. A marked degree of involution and fibrosis is present ($\times 175$)

epithelial appearance. The interstitial tissue was markedly increased in amount and was composed of loose fibro-areolar tissue in which there were scattered varying numbers of small lymphocytes (figs 1 and 2). In some sections, the fatty areolar tissue which had entirely supplanted the original thymic parenchyma showed numerous dense collections of lymphocytes in which remains of reticular cells or corpuscles of Hassall could not be seen. The fibrous capsule about the thymic fat body and sections of the posterior mediastinal wall revealed similar collections of lymphocytes (fig 3), and this seems good evidence that the lymphocytes seen in some of these glands were merely a part of the general process of lymphocytic accumulation in tissues, which is char-

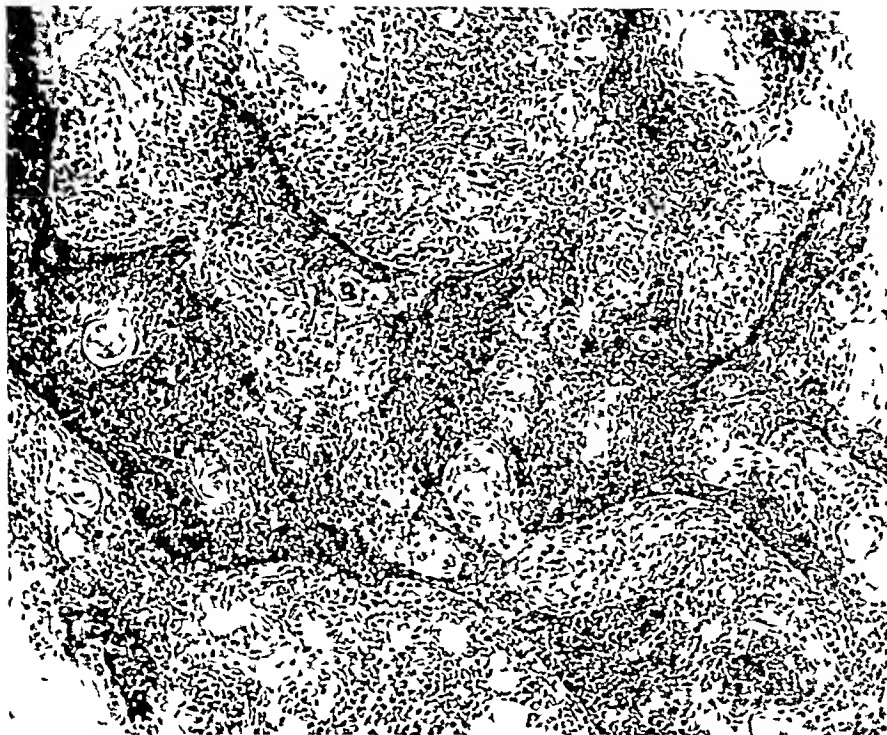


Fig 2—Section of thymus gland of a child, aged 6, who died of acute lymphatic leukemia. There is evidence of involution and infiltration of interstitial tissue with lymphocytes ($\times 150$)

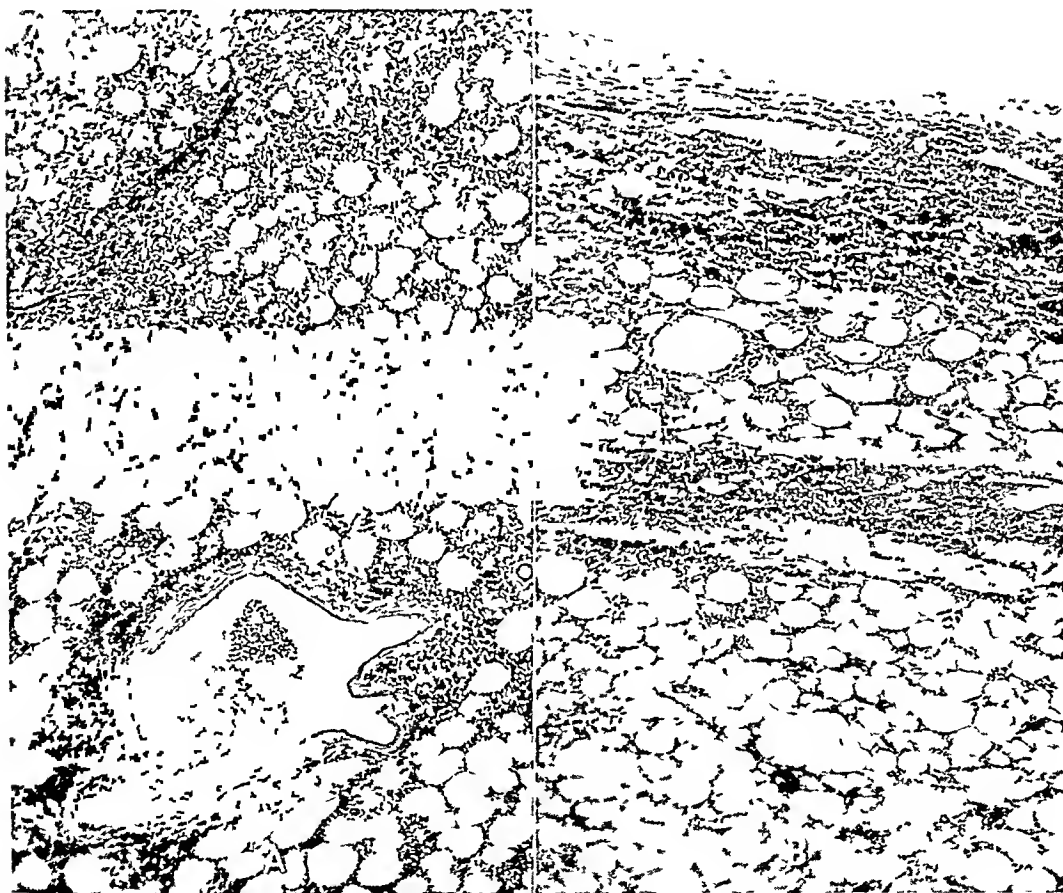


Fig 3—*A*, thymic fatty areolar tissue heavily infiltrated with lymphocytes in a man, aged 54, who died from lymphatic leukemia ($\times 100$), *B*, section of posterior mediastinal wall of the same patient, showing a nearly proportionate degree of lymphocytic infiltration ($\times 100$)

acteristic of the disease. In sections of glands in which involution was not complete, the corpuscles of Hassall appeared somewhat increased in number, this was probably a relative increase made apparent by the degeneration and disappearance of many small thymic cells. Most of the corpuscles showed hyaline degeneration, and only occasionally were newly formed corpuscles encountered. The entire process partook essentially of the nature of advanced involution such as one encounters in various disease processes and altered nutritional states. It is significant that the changes just described occurred as frequently in the glands of children as in those of adults and in them the factor of involution from age had not yet come into play. In the remaining cases of this group the thymus gland did not reveal gross abnormalities, and hence microscopic sections were available in only one case, that of a man, aged 50, who had had symptoms of acute lymphatic leukemia for

TABLE 2—Cases in Which the Thymus Gland Apparently Was Enlarged (Group 2)

Case	Diagnosis	Age, Years	Sex	Duration of Symptoms, Mo	Leukocytes	Lymphocytes, per Cent	Pathologic Changes in Thymus Mass
29	Aleukemic leukemia	5	M	5.5	2,800* 8,000*	70 92	Involution with fibrosis and diffuse lymphocytic infiltration, weight 50 Gm
30	Acute lymphatic leukemia (leukosarcoma)	2	M	1	32,800	80 88	Involution with fibrosis and diffuse lymphocytic infiltration, weight 215 Gm
31	Acute lymphatic leukemia (leukosarcoma)	23	M	4	297,000	94	Involution and lymphocytic infiltration, weight 470 Gm
32	Acute lymphatic leukemia (leukosarcoma)	8	M	1	55,000 232,000	86 89	Involution with fibrosis and diffuse lymphocytic infiltration, weight 255 Gm

* Lowest and highest counts

from three to four months. The section of the thymus gland showed a marked degree of involution, with degeneration and disappearance of a large portion of the cortex, and a corresponding degree of replacement by fibrous tissue.

Leukemia with Enlargement of the Thymus Gland—Group 2 (table 2) comprised a series of four cases, three in children and one in a man, aged 23. Three of these cases presented the picture of rapidly progressive acute lymphatic leukemia. In addition to the generalized tendency for lymphocytic accumulation within tissues, there was a tendency to maximal infiltration in only one or two sites, such as the mediastinal structures and kidneys. The result was huge enlargement of the kidneys and the mediastinal structures, the latter becoming matted together and appearing as if frozen to the lungs and pericardium (fig. 4). Because of this tendency to a sarcomatous type of proliferation in a condition which is essentially one of leukemia, the term leukosarcoma may well be applied as denoting perhaps the most malignant

form of true lymphatic leukemia. The anterior mediastinal mass in these cases was remarkable for its gross size. In the one case of aleukemia leukemia in this group the weight of the mediastinal mass was 50 Gm, while in the three cases of leukosarcoma the mediastinal tumors assumed huge proportions, weighing from 215 to 470 Gm. These appeared as huge mediastinal tumors which wrapped themselves about the pericardium and the great vessels. They were homogeneous, dull, white or yellowish white, and of rather firm consistence. The mass merged imperceptibly with the parietal pericardium to which it was adherent. When cut, it presented the same white appearance, and the



Fig 4—Sagittal section of anterior mediastinal mass, including the thymus, in a boy, aged 8, who died from leukosarcoma

lines of cleavage between the thymus gland and its capsule and between the capsule and the parietal pericardium could not be distinguished.

Numerous sections taken from various parts of the mass could not be distinguished histologically. Material from the center, in the region of the thymus gland, showed essentially the same histologic structure as that taken from the capsule and the attached pericardium. The normal structure of the thymus gland was entirely obliterated, there was no reticulum and there were no corpuscles of Hassall. There were dense collections of lymphocytes throughout the entire mass and a rather abundant stroma composed of dense fibrous tissue. The lymphocytes varied considerably in size and some contained mitotic figures. Here and there the lymphocytes were densely aggregated in small groups which stood out in sharp contrast with the remainder of the parenchyma.

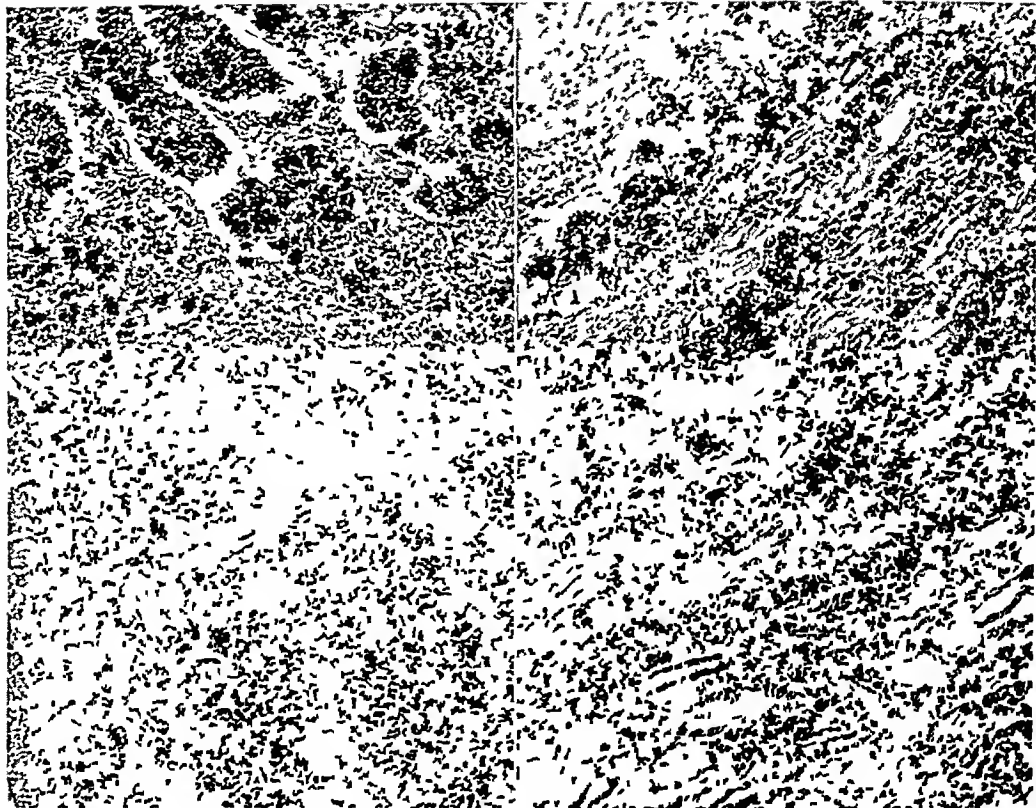


Fig 5—*A*, thymus of a child, aged 2, who died from leukosarcoma. Involution and fibrosis with diffuse lymphocytic infiltration are present ($\times 150$), *B*, kidney of the same patient, also showing lymphocytic infiltration ($\times 150$)

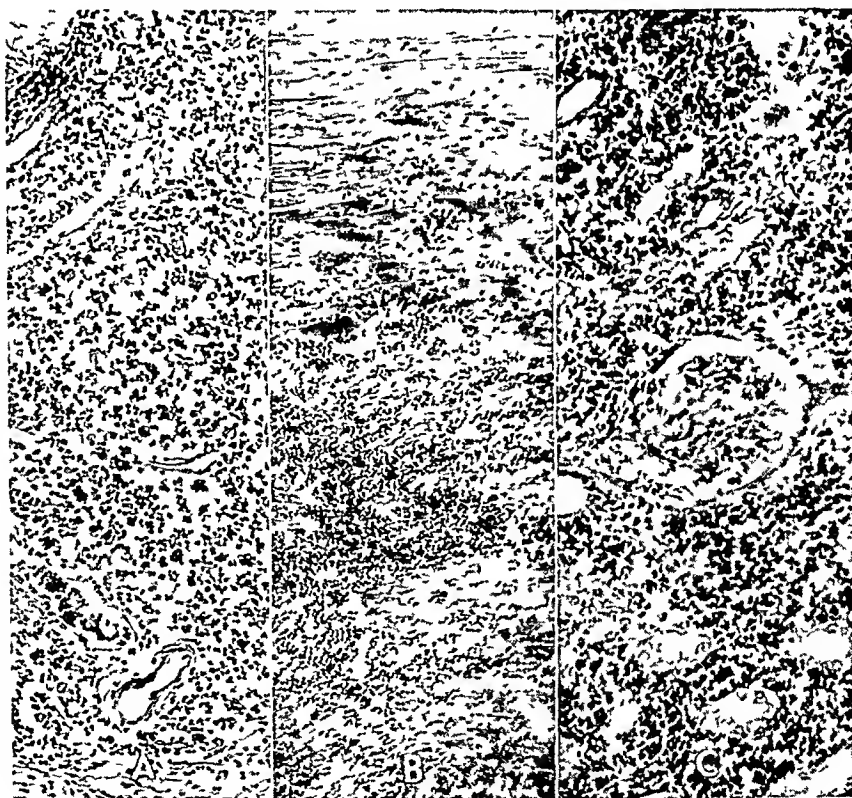


Fig 6—*A* thymus gland of a child, aged 8. There is evidence of marked involution with fibrosis and diffuse lymphocytic infiltration ($\times 175$), *B*, diaphragm ($\times 150$) and *C* kidney of the same patient showing proportionate degrees of infiltration with lymphocytes ($\times 175$)

In each of the three cases of leukosarcoma there was also tremendous enlargement of the kidneys, the liver and the spleen. The kidneys of one child aged 2, weighed 545 Gm, in another child, aged 8, both kidneys weighed 710 Gm and in the third case, that of a man, aged 23, the kidneys weighed 1 046 Gm. The liver and the spleen were nearly proportionately enlarged. These organs were opaque and white, because of the dense collections of lymphocytes, and they presented evidence of extensive hemorrhage into their substance. Histologic sections of the kidneys and of the liver revealed extensive and dense infiltration with lymphocytes identical morphologically with those seen in the mediastinal mass. In part of the section the infiltration with lymphocytes was so dense as entirely to obliterate the normal structures of the organ. Such fields presented a histologic appearance almost identical with that of the mediastinal mass, except that the latter contained a greater amount of interstitial tissue. The parenchymatous elements of the kidneys and the liver revealed extensive granular degeneration. Sections from other tissues, such as those of the gastrointestinal tract and even the diaphragm, showed that they also were affected to a variable degree by the general infiltrating process (figs 5 and 6). General lymphoid hyperplasia was present in all cases of the group.

COMMENT

In the entire series of thirty-two cases of various types of lymphatic leukemia enlargement of the thymus gland was found in only four cases. In the remaining twenty-eight cases the thymus gland either did not show notable abnormality or showed gross or histologic evidence of varying degrees of involution. That ten of the cases were in children emphasizes the fact that the involution was not always that due to physiologic retrogression associated with age, but that it was a reaction of the thymus gland to the disease process. It is not possible of course, to say just what influences the thymus gland in leukemia. The altered nutritional state must be considered as one of the possible factors productive of the process of involution since the relation of disturbed nutrition to pathologic involution of the thymus gland is now well established. What seems more interesting, however, is the striking involution of the thymus gland in a disease the essential feature of which is a tendency to hyperplasia of lymphoid tissues. This, indeed, brings into question the often quoted concept of the true lymphatic nature of the thymus gland and its small thymic cells. That the small thymic cells should react so unlike the lymphocytic elements elsewhere in the body suggests that they may be of inherently different nature, unless one postulates an overwhelming influence in leukemia productive of thymic involution and one sufficient to overcome the general stimulus

to lymphoid hyperplasia. I have no reason to believe that the latter is the case. The more direct interpretation of a different biologic nature of the small thymic cells and the blood lymphocytes seems more reasonable. I have already quoted evidence that has been adduced by many observers pointing to the epithelial source of the small thymic cells. The reactions of the thymus gland in leukemia also indicate a biologic difference, hence a different histogenetic source of the thymic cells from that of the blood lymphocytes does not seem unlikely.

The occurrence of an enlarged thymus gland in the four cases of leukemia would at first seem to militate against this hypothesis. However, the histologic features of these cases, too, point to an advanced degree of involution with secondary infiltration of the organ by lymphocytes. The lymphocytes in these glands appeared as densely aggregated in the connective tissue and capsule of the organ as in the parts normally occupied by the thymic parenchyma. Furthermore, the degree of infiltration in the thymus gland in the three cases of leukosarcoma paralleled that in other nonlymphatic organs, such as the kidney and the liver. It seems obvious from this that enlargement of the thymus gland in leukemia, when it does occur, represents merely a part of the tendency to infiltration of organs by lymphocytes that is so characteristic of this disease. In other words, the thymic enlargement in these cases does not represent true hyperplasia of the small thymic cells, but is due to nonspecific infiltration with lymphocytes, such as frequently affects the kidneys, liver, skin and other nonlymphatic structures in the body.

SUMMARY AND CONCLUSIONS

The thymus gland is rarely enlarged in lymphatic leukemia, the predominant tendency in this disease is in the direction of involution of the organ. When thymic enlargement does occur in leukemia, it usually parallels the degree of infiltration in other organs. Such enlargement of the thymus gland is not due to hyperplasia of the small thymic cells, but is due to infiltration by lymphocytes, the process is identical with that leading to infiltration of other nonlymphoid organs.

The reaction of the small thymic cells in lymphatic leukemia differs from that of the blood lymphocytes and suggests a difference in the biologic nature of the small thymic cells and the blood lymphocytes. A different histogenetic source of the small thymic cells from that of the blood lymphocytes may be inferred.

SERUM MENINGITIS *

DOUGLAS GOLDMAN, M D

CINCINNATI

The stimulus for undertaking the investigation here recorded was the occurrence of several cases of aseptic meningitis discovered at autopsy in patients who had received serum injections into the spinal theca. Most of the cases were instances of fatal tetanus, but a case of cerebral hemorrhage clinically resembling meningitis in a young adult is also on record.

Most of the modern textbooks fail to mention the occurrence of aseptic meningitis following serum injections into the spinal theca, the few that do devote to it a few sentences without emphasis. In the literature references to the phenomenon are rather rare, but may be found even in articles of twenty years ago¹. Recently interest in the subject has grown because induction of aseptic meningitis has been found of use in the treatment for schizophrenia and other mental states (Carioll, Kubitschek and Carmichael). A further experimental study in laboratory animals, with a review of as much of the literature as was available, seemed to be of timely interest.

Purves-Stewart² pointed out that "an abundant polynuclear pleocytosis" of the spinal fluid can be produced by the injection of sterile salt solution or sterile suspensions of colored particles into the spinal theca of monkeys. He mentioned no study of the lesions produced and relegated the fact to a footnote in the edition of his book published in 1911. Szecsi³ made a study of the aseptic meningeal reaction to salt solution, which he reported in 1912.

Flexner and Amoss⁴ noted the occurrence of aseptic meningitis in experimental animals following intrathecal administration of serum. They stated "Introduction of sterile alien blood serum into the subarachnoid space causes an aseptic inflammation of mild degree that reaches its maximum in twenty-four hours and then subsides. The

* Submitted for publication, Dec 16, 1929

* From the Department of Pathology, University of Cincinnati, and Cincinnati General Hospital

1 Widal et al, quoted by Frommel, E. *Schweiz med Wchnschr* **57** 873, 1927

2 Purves-Stewart, Sir James. *Diagnosis of Nervous Diseases*, ed 3, London, Arnold & Company, 1911

3 Szecsi, S. *Ztschr f d ges Neurol u Psychiat* **60** 481, 1912

4 Flexner, S, and Amoss, H L. *J Exper Med* **20** 249, 1914, **25** 525, 1917

inflammation is marked by emigration into the pia-arachnoid, ventricles and choroid plexus of polymorphonuclear leucocytes chiefly and by the escape of plasma." These investigators later found that, in addition to alien serum, normal homologous serum, physiologic solution of sodium chloride, Ringer's solution and sometimes even homologous spinal fluid caused a meningeal reaction when injected into the spinal theca. They were producing aseptic meningitis in monkeys to cause localization of poliomyelitic virus in the nervous system following intravenous inoculation. Flexner⁵ stated that aseptic meningitis is of negligible importance in the treatment for meningitis.

The pharmacologic effect of intrathecal injections of serum is set forth in a masterful exposition by Auer⁶.

Ingleton⁷ reported that there was a rather constant cellular reaction in the spinal fluid following intrathecal injection of antitetanic serum in cases of active tetanus. He withdrew second samples of fluid twenty-four hours after the injections of serum and found an average cell count of 400 per cubic millimeter, with 95 per cent polymorphonuclears. Postmortem examination in fatal cases of his series showed definite aseptic meningitis of varying intensity in each instance.

Leishman and Smallman⁸ mentioned that one of them saw specimens of spinal cords removed after death in cases of tetanus, in which there was definite evidence that meningitis had followed the lumbar punctures. Their idea seemed to be that the meningitis was the effect of contamination carried into the theca by the needle. It apparently did not occur to them that the reaction could be aseptic and directly the result of the injections of serum.

The history of the "Medical Department of the U. S. Army in the World War"⁹ reprints instructions given to medical officers concerning tetanus in which it is mentioned that intraspinal serum treatment may be followed by turbid spinal fluid, which is of relatively slight importance.

Ayer¹⁰ in a study of the pathology of experimental meningitis discussed aseptic meningitis in some detail. He stated that aseptic menin-

5 Flexner, S. Mode of Infection, Means of Prevention and Specific Treatment of Epidemic Meningitis, Monograph of the Rockefeller Institute, New York, 1917.

6 Auer, J. J. Exper. Med. **21** 43, 1915.

7 Ingleton, J. Roy. Army M. Corps **26** 234, 1916.

8 Leishman, Sir W. B., and Smallman, A. B. Lancet **1** 131, 1917.

9 The Medical Department of the U. S. Army in the World War, Washington, D. C., Government Printing Office, 1927, vol. 11, pt. 1, p. 284.

10 Ayer, J. B. A Study of Experimental Meningitis. 2. Pathological Study of Experimental Meningitis from Subarachnoid Inoculation, Monograph of the Rockefeller Institute, no. 12, March 25, 1920.

gitis may be expected following intrathecal injection of almost any foreign substance and mentioned among other substances capable of causing this reaction autogenous, homologous and heterologous serums. In his article, he gave two protocols showing the acute and residual effects of intrathecal injections of serum into animals. His results are in no way different from those recorded in this article. Ayei's experiments are the only ones found that represent a careful investigation of serum meningitis per se.

Weed and Wegeforth¹¹ studied the effects of irrigations of the subarachnoid space. Physiologic solution of sodium chloride was found to be much more toxic in irrigations than a modified Ringer's solution.

Wegeforth and Essick¹² found that various antiseptics caused an aseptic meningitis. This observation is in agreement with the results of other workers who have studied this phase of the subject.

Wertheimer¹³ reported a case of aseptic meningitis following spinal anesthesia.

Stone¹⁴ mentioned the occasional occurrence of "so-called" serous meningitis following intravenous injection of alien serum. He did not seem to relate the meningeal reactions to intrathecal injections of serum. Shaw and Shapland¹⁵ spoke of "tetanism in meningitis" and cited two cases which, from the histories given, might well have been tetanus with meningitis secondary to intraspinal medication.

Boyd¹⁶ cited the work of Purves-Stewart and of Ingleton in mentioning that aseptic inflammation of the meninges occurs.

Kimura¹⁷ used Flexner's method of producing aseptic meningitis with serum in a study of the penetration of drugs and biologic products into the spinal fluid.

Young and Alpers¹⁸ found a relatively small cellular increase in the cells of the cerebrospinal fluid following the injection of Swift-Ellis serum into ventricles, cistern and lumbar sac.

11 Weed, L. H., and Wegeforth, P. *J. Pharmacol. & Exper. Therap.* **13**: 317, 1919.

12 Wegeforth, P., and Essick, C. R. *J. Pharmacol. & Exper. Therap.* **13**: 335, 1919.

13 Wertheimer, P. *Lyon chir.* **19**: 387, 1922.

14 Stone, W. J. *Treatment of Tetanus*, *J. A. M. A.* **78**: 1939 (June 24), 1922.

15 Shaw, H. B., and Shapland, C. D. *Brit. M. J.* **1**: 183, 1923.

16 Boyd, W. *The Cerebrospinal Fluid*, New York, The Macmillan Company, 1920.

17 Kimura. *Japan M. World* **3**: 67 (April 15), 1923.

18 Young, A. W., and Alpers, B. I. *The Protein and Cellular Content of Cerebrospinal Fluid. Changes in Fluid Following Intraspinal, Intracistern and Intraventricular Therapy with Swift-Ellis Serum*, *Arch. Neurol. & Psychiat.* **12**: 537 (Nov.) 1924.

In his study of meningeal irritability, Kasahara¹⁹ investigated the effect of various serums and "physiologic" solutions on the cell count of the cerebrospinal fluid in rabbits. He found that fresh serum called forth a greater cellular response than inactivated serum, and that heterologous spinal fluid was less irritating than any of the 'physiologic' solutions. He did not record cultures of the spinal fluids and made no study of the lesions that he produced.

Golla and Herrmann²⁰ noted that aseptic meningitis follows injection of air into the subarachnoid space. Their studies showed no similar effect following lumbar puncture alone.

Frommel²¹ discussed at length aseptic serum meningitis occurring in the course of treatment for cerebrospinal fever. He cited the work of several French investigators. According to him there are two kinds of reactions to serum on the part of the meninges, difficult to differentiate in practice. The first is the simple reaction of the theca to a foreign substance of any sort, and the second is a local manifestation of a general sensitive state (anaphylaxis) occurring only after a latent period following sensitization. He regarded serum meningitis as definitely harmful to the prospects of a patient receiving treatment for infectious meningitis and advised cessation of intrathecal injections of serum when the spinal fluid has been cleared by thorough treatment at the beginning of the disease. Frommel deplored the general lack of recognition of this condition in the course of meningitis of infectious origin.

In the last few years several reports of the therapeutic effect of aseptic meningitis in human beings suffering from mental disorders, particularly schizophrenic states, have appeared in American journals.

The first report of such work is in an article by Carroll²² published in 1923. Several investigators have taken up this work²³. The experiments of Kubitschek and Carmichael²⁴ are the most recent and represent the most thorough study of the physical aspects of this form of treatment. Inactivated horse serum was injected intraspinaly into patients suffering from dementia praecox in doses of 20 cc after a somewhat larger amount of fluid was drawn off. The cell count of the spinal fluid invariably rose, reaching its height in from twenty-four to forty-eight hours. After a single injection, from 200 to 5,500 cells per

19 Kasahara, M. Experimental Study in Meningeal Irritability, *Am J Dis Child* 28:407 (Oct) 1924

20 Golla, F, and Herrmann G. *Med Klin* 22 1951, 1926

21 Frommel, E. *Schweiz med Wchnschr* 57 873, 1927

22 Carroll, R S. *New York M J* 118 407 (Oct 3) 1923

23 Carroll, R S, Barr, E S, Barry, R G and Matzke, D. *Am J Psychiat* 4 673, 1924-1925

24 Kubitschek, P E, and Carmichael, F A. *Am J Psychiat* 8 27, 1928

cubic millimeter were found, mostly polymorphonuclears in the early stage of the reaction. After seven or more days, the count was much reduced, and most of the cells were lymphocytes. A leukocytosis of the blood ran parallel with that in the spinal fluid. Second and subsequent injections after a week or more were associated with more severe types of reaction in some cases in which the spinal fluid pressure and cell count were unusually high (40 mm of mercury and 13,000 cells). The patients with such severe meningeal reactions were always relieved by cistern puncture. Systemic anaphylactic manifestations were controlled with epinephrine.

Recently, Bagley²⁵ reported experiments on the effect of blood in the cerebrospinal fluid. He found a definite microscopic cellular reaction to the presence of the blood, most marked at the site of the injection (subdural). His experiments, however, dealt with the more prolonged and severe types of bleeding into the subarachnoid space.

MATERIALS AND METHODS

Dogs were used in all of the experiments here recorded. They were considered most suitable because of the ease with which the cisterna magna can be reached with a needle. Lumbar puncture in the dog is unsatisfactory, because the spinal cord extends to the first sacral vertebra.

For the operation of cistern puncture, the animal was tied to the table with the belly down, and the back of the head and neck were shaved in a wide area. Ether anesthesia was used in every case. No postoperative pulmonary complications were encountered following the anesthesia, probably because in no case was the anesthesia carried on for more than ten minutes. The shaved area was cleansed with iodine and alcohol or with iodine and 5 per cent phenol. The punctures were done with a 19-gage needle attached to an all-glass syringe. The cisterna could in most cases be entered quickly and easily by thrusting the needle through the skin at the level of the transverse process of the atlas, pointing forward at an angle of 45 degrees to the perpendicular. The cisterna is usually reached at a depth of from 1.5 to 2 cm depending on the size of the animal used. As a precautionary measure to prevent injury to the brain stem as a result of inserting the needle too far, slight suction is made with the syringe just as it enters the cistern.

From 5 to 8 cc of clear cerebrospinal fluid can be removed from a normal animal without causing any unfavorable symptoms. In making injections into the cisterna magna, it is useful to employ a three-way stopcock to which the needle and two syringes can be connected, one empty syringe to aspirate the fluid and one syringe containing the fluid to be injected. When a suitable amount of fluid is withdrawn, the injection is made by turning the stopcock and allowing the injected liquid to run into the cisterna by its own weight. Aspiration of the cerebrospinal fluid is necessary, because with the animal ventral side down gravity does not help the fluid to flow upward through the needle.

Cell counts and globulin determinations were done on all but grossly bloody fluids. Chemical blood tests (Meyer's) were done on all fluids. When a trace

25 Bagley, C. Blood in the Cerebrospinal Fluid. Resultant Functional and Organic Alterations in the Central Nervous System, *Arch Surg* **17** 18 (July) 1928.

of blood was found chemically, counts of both red and white cells in the spinal fluid were made. The most convenient way to do this is to use a double-ruled counting chamber and count the cells in laked (acetic acid) and unlaked specimens of spinal fluid, the difference representing the number of red corpuscles. Counts of less than 1,500 red blood cells per cubic millimeter were considered of no significance, since less than $\frac{1}{3}$ 000 the volume of fluid withdrawn could be blood, and this probably was derived from tissues through which the needle must pass to reach the cistern. Under ordinary circumstances, with a ratio of about 1 500 of white cells to red cells in the blood, 1,500 red corpuscles per cubic millimeter account for only 3 leukocytes in a similar volume, a number which is of no significance in a spinal fluid cell count. In addition, all abnormal and most normal fluids were cultured in two or three different mediums to rule out septic meningitis.

Most of the experiments consisted of a single injection of serum or other given fluid followed in a variable period by a second puncture to discover the changes wrought by the injection. The animal was then killed, and the brain removed. Some experiments involved more than two punctures, and some animals were saved for three or more weeks after unsatisfactory experiments and then used again. None of the animals suffered any ill effects from either cistern puncture or injection. Occasionally, an animal was overcome by the anesthetic and had to be resuscitated with artificial respiration. Removal of the brain was facilitated and rendered bloodless by bleeding the animal from the femoral artery before death or by cutting the great vessels of the thorax and allowing the animal to bleed internally.

The quickest and simplest way to remove the dog's brain is to make a trephine hole in the temporal region of the skull and then rongeur the skull away from the brain. The organ is then lifted out while the nerve roots are cut from before backward. All brains were fixed in toto in formaldehyde (4 per cent) for a varying period, not less than two weeks. Paraffin sections were made of pieces cut from at least four different regions and stained by the usual hematoxylin-eosin method.

The serums used for injection were the commercial products of reliable manufacturers, identical with the products used therapeutically in human beings.

EXPERIMENTS AND RESULTS

Control Experiments—As control experiments, simple cisternal puncture, reinjection of spinal fluid and injection of salt solution were done. Simple cisternal puncture and withdrawal of cerebrospinal fluid had only a slight effect on the spinal fluid drawn off subsequently, and this was very likely secondary to slight bleeding at the point of the first puncture after the needle was withdrawn.

EXPERIMENT 2—January 10, at 3 30 p. m., with the dog under ether anesthesia, cistern puncture yielded 7 cc of crystal clear fluid. No injection was made. A culture of the fluid was negative. The fluid contained five lymphoid cells per cubic millimeter. No symptoms resulted from the puncture. January 11, at 8 a. m., with the dog under ether anesthesia, a second puncture was done, the first portion of fluid obtained was slightly blood tinged, but after this clear fluid with a faint yellow color was obtained. A culture of the fluid was negative. It contained 34 cells per cubic millimeter, chiefly of lymphoid type. The animal was bled 500 cc from the femoral artery, and sufficient ether was administered to kill it. The brain was removed and fixed in formaldehyde. Slight hemor-

rhage was caused in the cerebellopontile angle in removing the brain. No gross abnormalities could be detected. Microscopically, the brain and meninges had no pathologic characteristics.

Reinjection of the spinal fluid just withdrawn caused a slight transient reaction in the spinal fluid. This reaction was more than might be expected, but the experience of many punctures in these animals indicates that no intrathecal injection can be made without causing some reaction.

EXPERIMENT 16—February 14, at 3 p. m., with the animal under ether anesthesia, cistern puncture yielded 5 cc of crystal clear fluid, of which 2.5 cc was reinjected slowly. The fluid contained 5 cells per cubic millimeter of lymphocytic type. A chemical test for blood was negative. February 15, at 3 p. m., with the animal under ether anesthesia, cistern puncture yielded 5 cc of slightly turbid fluid. A culture of the fluid was negative. The fluid contained 750 cells per cubic millimeter, made up of equal numbers of polymorphonuclears and lymphocytes, 240 red corpuscles per cubic millimeter were present, and tests for globulin and blood were positive. February 18, with the dog under ether anesthesia, cistern puncture yielded 5 cc of clear colorless fluid. It contained 8 lymphocytes per cubic millimeter. The chemical test for globulin was negative, and the test for blood faintly positive. The animal was saved for further experiment, since it was felt that sections would show no significant changes.

Injection of physiologic (0.9 per cent) solution of sodium chloride caused a more profound reaction than reinjection of spinal fluid.

EXPERIMENT 14—February 4, at 3:30 p. m., with the dog under ether anesthesia, cistern puncture yielded 5 cc of crystal clear fluid, 5 cc of saline solution (0.9 per cent) was injected. The fluid contained 10 cells per cubic millimeter. Chemical tests for globulin and blood were both negative. February 5, at 8 a. m., with the animal under ether anesthesia, cistern puncture yielded 6 cc of slightly turbid, colorless fluid. The thoracic vessels were cut to cause internal bleeding. The brain was removed and fixed in formaldehyde. The cistern fluid contained 766 leukocytes per cubic millimeter, made up of equal numbers of polymorphonuclears and lymphocytes, and 64 red corpuscles per cubic millimeter. A faintly positive chemical test for blood, and a positive test for globulin were noted. The animal had shown no symptoms in the course of the experiment. Microscopic sections of the brain and meninges showed a moderate invasion of the pia by polymorphonuclear leukocytes and lymphocytes and some exudation of these cells into the subarachnoid space over both cortex and base. There was some cellular invasion of the stroma of the choroid plexus of the fourth ventricle and moderate denudation of the epithelium covering the plexus in several places. Similar results were obtained in another animal subjected to a similar experiment.

Effect of Bloody Spinal Fluid—Contrary to what might be expected, a puncture yielding grossly bloody fluid resulted in changes much less marked than those caused by salt solution.

EXPERIMENT 7—January 22, in the afternoon, with the dog under ether anesthesia, cistern puncture yielded grossly bloody fluid. The animal reacted well from the anesthetic. In the morning, January 23, cistern puncture under ether anesthesia yielded 5 cc of somewhat yellowish fluid containing many red corpuscles. A culture of the fluid was negative. The animal was killed by cutting of the thoracic vessels. The brain was removed and fixed in formaldehyde. Microscopic examination of various parts of the brain and spinal cord showed only slight infiltration of mononuclear cells and a few polymorphonuclears in the neighborhood of blood vessels. The choroid plexus appeared normal.

Horse Serum Injections—Intrathecal injections of horse serum were found to produce a considerable leukocytosis in the spinal fluid within twenty-four hours. The reaction subsided in the next two or three days. A slight residual pleocytosis was found in one animal that had been spared, after three weeks. A second injection several weeks after a first injection of serum resulted in a milder type of reaction than did the first injection. (In connection with this fact, we are reminded of the dog's low susceptibility to anaphylactic shock.)

EXPERIMENT 13—January 28, at 3 p m, cistern puncture yielded 4 cc of crystal clear fluid, 3 cc of horse serum was injected. A culture of the fluid was negative. The fluid contained 15 lymphocytes per cubic millimeter. A chemical test for blood was faintly positive. January 29, at 8 15 a m, with the dog under ether anesthesia, cistern puncture yielded 5 cc of slightly cloudy fluid. More ether was administered, and the thoracic vessels were cut to kill the animal. The brain was removed and fixed in formaldehyde. The fluid contained 1,128 leukocytes per cubic millimeter, made up of equal numbers of polymorphonuclears and lymphocytes. No red corpuscles were present, and the chemical test for blood was negative. A test for excess globulin was positive. A culture of the fluid was sterile. Study of microscopic sections showed widespread infiltration of the pia and subarachnoid space with an exudate consisting mainly of polymorphonuclear cells, but including a few lymphocytes and mononuclears. The reaction was heaviest over the brain stem and cerebellum, as might be expected from a cisternal injection. The cerebellar cortex was found invaded by the inflammatory reaction, with slight destruction of brain substance in a few small areas. The choroid plexus showed moderate invasion of the stroma by lymphocytes.

EXPERIMENT 10—January 8, at 3 30 p m, with the dog under ether anesthesia, cistern puncture yielded 6 cc of crystal clear fluid, 5 cc of the horse serum was slowly injected. The animal reacted well from the anesthetic. A culture of the fluid was negative. The fluid contained 12 cells per cubic millimeter. A chemical test for globulin was negative. January 10, at 8 30 a m, with the animal under ether anesthesia, cistern puncture yielded at first blood-tinged fluid and then crystal clear fluid. A culture of the fluid was negative. The chemical test for blood was negative, that for globulin, faintly positive. Thirty-nine cells per cubic millimeter were present, mostly lymphocytes. The animal was bled 750 cc from the femoral artery, and enough ether given to kill it. The brain was removed and fixed in formaldehyde. Microscopic sections showed a mild meningeal reaction consisting of polymorphonuclear and mononuclear cells. The reacting cells were most numerous near blood vessels. There was increase in cellularity of the choroid stroma with distortion and denudation of portions of the choroid ependyma.

EXPERIMENT 6—December 28, with the dog under ether anesthesia, cistern puncture yielded 5 cc of slightly blood-tinged fluid, and 3 cc of horse serum was injected. The animal reacted well from the anesthetic. A culture of the fluid was negative. January 31, at 8 30 a m, with the dog under ether anesthesia, cistern puncture yielded clear fluid, 5 cc of horse serum was injected. The fluid contained 22 lymphocytes per cubic millimeter. Tests for globulin and blood were negative. February 1, at 8 30 a m, with the animal under ether anesthesia, cistern puncture yielded slightly turbid fluid. The thoracic vessels were cut, and sufficient ether given to kill the animal. The brain was removed and fixed in formaldehyde. A culture of the fluid was negative. The chemical

test for blood was negative, that for globulin, positive. There were 650 leukocytes per cubic millimeter, made up of equal numbers of polymorphonuclears and lymphocytes. Microscopic examination of the brain and meninges showed a moderate reaction consisting of polymorphonuclear and mononuclear cells in the pia. The reacting cells were frequently grouped in the neighborhood of the blood vessels. The most intense reaction was in the region of the brain stem. The stroma of the choroid plexus of the fourth ventricle showed increase in cellularity, but the ependyma was of practically normal appearance.

Therapeutic Serum—Refined forms of horse serum, such as are used in the treatment for meningitis and tetanus, cause changes differing in no way from those caused by the unrefined horse serum.

EXPERIMENT 17—February 26, at 3 30 p. m., with the dog under ether anesthesia, cistern puncture yielded 5 cc of clear fluid, 3.5 cc of tetanus antitoxin (2,100 units) was injected. The fluid removed contained 10 cells per cubic millimeter. Tests for blood and for globulin were negative. February 27, at 8 15 a. m., with the animal under ether anesthesia, cistern puncture yielded 4 cc of slightly turbid, somewhat yellow fluid. The thoracic vessels were cut, and sufficient ether administered to kill the animal. The brain was removed and fixed in formaldehyde. A culture of the cistern fluid was negative. Leukocytes numbered 1,880 per cubic millimeter, polymorphonuclears constituting 60 per cent and lymphocytes, 40 per cent. Chemical tests for globulin and blood were both positive. It was believed that the blood was of no significance and had its origin outside the cistern. Microscopic sections showed moderately heavy invasion of the pia and subarachnoid space with leukocytes, over both cortex and brain stem. Some cellular exudate was found in the cerebral ventricles. There was increased cellularity of the choroid stroma.

EXPERIMENT 19—February 19, at 3 p. m., with the dog under ether anesthesia, cistern puncture yielded 5.5 cc of clear fluid, 5 cc of antimeningococcus serum was injected. The fluid contained 8 cells per cubic millimeter. The chemical test for globulin was negative, and that for blood, faintly positive. February 20, at 8 30 a. m., with the animal under ether anesthesia, cistern puncture yielded slightly turbid fluid with a faint yellowish tinge. A culture of the fluid was negative. Leukocytes numbered 2,230 per cubic millimeter, and were made up of equal numbers of polymorphonuclears and lymphocytes, 2,500 red corpuscles per cubic millimeter were counted, and the test for blood was positive. The blood was considered an accidental contamination. February 21, at 2 p. m., with the animal under ether anesthesia, cistern puncture yielded almost clear fluid with a slight yellowish color, 172 leukocytes and 2,100 red corpuscles per cubic millimeter were counted. The chemical test for globulin was faintly positive.

Tricresol—Tricresol was injected in one experiment because it is the most commonly used preservative for commercial serums. It produced a marked leukocytosis of the spinal fluid, but the histologic picture of the meninges showed a less marked reaction than that following injections of serum.

EXPERIMENT 15—February 12, at 2 p. m., with the dog under ether anesthesia, cistern puncture yielded 7 cc of clear fluid, 5 cc of the spinal fluid was mixed with 1 cc of 24 per cent cresol by means of the three-way stopcock (resulting mixture contained about 0.4 per cent cresol in spinal fluid) and the mixture injected. The spinal fluid contained 2 cells per cubic millimeter. February 13,

at 8 30 a m, with the animal under ether anesthesia, cistern puncture yielded 6 cc of slightly turbid fluid. The animal was killed, and the brain removed and fixed in formaldehyde. The fluid contained 1,365 leukocytes per cubic millimeter, 320 red corpuscles per cubic millimeter were counted, and the chemical test for blood was positive. The test for globulin was faintly positive. Microscopic sections showed a moderate reaction of polymorphonuclear cells and lymphocytes in the pia and some edema of the meninges over the cortex and brain stem. There was moderate invasion of the stroma of the choroid plexus of the fourth ventricle with polymorphonuclear leukocytes and lymphocytes, and some swelling and denudation of the ependymal covering of the plexus.

TABLE 1—*Effect of Intraspinal Injection on the Cell Count of the Spinal Fluid*

Exper No	Substance Injected	Time After Injection	Spinal Fluid Cell Count, per Cu Mm	Histologic Reaction
8	Horse serum	17 hours	6,450	(No sections)
12	Horse serum	18 hours	978	Mild acute meningitis
13	Horse serum	17 hours	1,128	Acute meningitis
10	Horse serum	41 hours	39	Subsiding meningitis
4	Horse serum	5 days		Mild subacute meningitis
6	Horse serum, 2d	24 hours	650	Subacute meningitis
5	Horse serum, 2d	24 hours		Subacute meningitis
17	Antitetanus serum	17 hours	1,180	Acute meningitis
18	Antimeningitis serum	18 hours	5,220	Acute meningitis
19	Antimeningitis serum	18 hours	2,230	(No sections)
19		40 hours	172	
20	Antimeningitis serum	5 days	34	Subacute meningitis
11	Simple puncture	17 hours	34	Normal, no reaction
16	Spinal fluid	24 hours	750	(No sections)
16		4 days	8	
22	Spinal fluid	18 hours	250	Normal, no reaction
14	Salt solution	17 hours	765	Mild acute meningitis
9	Salt solution	17 hours	944	Mild acute meningitis
15	Cresol, 0.4 per cent	19 hours	1,365	Mild acute meningitis

TABLE 2—*Experiment 21—Effect of Multiple Intraspinal Injection of Antitetanus Serum on the Cell Count of the Spinal Fluid*

Date and Time	Antitetanus Serum Injected, Cc	Spinal Fluid Cell Count, per Cu Mm
6/18, 8 15 a m	2 0	6
6/18, 2 45 p m	2 5	12,240
6/19, 8 30 a m	2 0	3,120
6/19, 3 00 p m	2 5	1,740
6/20, 8 00 a m	3 5	1,480
6/20, 2 30 p m, killed	0 0	2,550
Microscopically, severe meningitis		

COMMENT

The results of these experiments are in agreement with those of other investigators. It was attempted to rule out all possibility of infectious meningitis by rigid adherence to aseptic technic and by culture of the cerebrospinal fluids obtained from the animals. It is hardly likely, therefore, that other than aseptic meningitis was present.

Various serums affected the meninges similarly. All called forth a polymorphonuclear reaction in the meninges and spinal fluid. The

intensity of the reaction varied from one animal to another and seemed, within limits, not to be related to the amount of serum injected or other controllable factors. It is significant that spinal fluid leukocytosis is always associated with a cellular reaction in the meninges. The experiments with serums rather definitely indicated that the cell content of the cerebrospinal fluid tends to diminish more rapidly and sooner than the meningeal reaction. That second injections had such small effect in dogs is not surprising, since the dog is not very susceptible to anaphylaxis.

The animals showed no unusual symptoms in clean-cut experiments. Occasionally, it was noted that an animal was somewhat more active following injection of the serum, but usually the attendant was the only one who could note the difference in behavior. The serum caused no febrile reaction in the dogs.

Some animals, the protocols for which were not recorded, were subjected to multiple injections and punctures without adverse effect (table 2).

The effect of the injection of salt solution and cresol calls for no comment. The reaction to the reinjection of spinal fluid was so mild and transient that it is of little more than theoretical significance.

It is particularly in diseases such as tetanus or in diseases with meningeal symptoms but without actual meningitis that repeated intrathecal injection of large doses of serum may lead to confusion in diagnosis and at times to actual harm to patients so treated. Recognition of the effect of serum and other sterile fluids on the meninges will serve to dispel this confusion. In cases of infectious meningitis in which serum treatment is used, daily observation of the condition of the spinal fluid is necessary to regulate the therapy, for continued use of serum is not without harmful effects in the absence of infection necessitating its use. There is, however, no contraindication to the use of therapeutic serums intrathecally when the hazard of the disease is greater than that of the serum which promises relief.

CONCLUSIONS

Aseptic meningitis has received scant recognition in the textbooks and only occasional serious consideration in the literature.

Intrathecal injections of serum produce spinal fluid leukocytosis and an accompanying aseptic meningitis with great regularity in experimental animals.

This aseptic meningitis is of short duration and produces no permanent changes of any importance in the meninges or nervous system.

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CEREBROSPINAL AND OCULAR FLUIDS IN
EXPERIMENTAL JAUNDICE IN DOGS*

HARRY L. SEGAL, M.D.

AND

JEROME GLASER, M.D.

ROCHESTER, N. Y.

Recent studies on the cerebrospinal fluid of infants,¹ indicating the frequency of xanthochromia, have stimulated further investigation of the relationship of xanthochromia in the spinal fluid to clinical jaundice. It occurred to us to determine whether xanthochromia could be produced or bilirubin caused to appear in the spinal fluid in experimental jaundice in dogs. We also wished to determine if the degree of jaundice had any relationship to the xanthochromia that might occur in the cerebrospinal fluid. Further, we desired to learn whether nuclear (kern) icterus,² i.e., a yellow staining of variable intensity of certain of the basal ganglions, such as occurs in some cases of icterus neonatorum, could be produced experimentally. The exact nature of the pigment in the nerve cells in this condition has not been shown. It is generally assumed that the pigment is biliary in origin, but the possibility that it is a lipochrome has been suggested.³ In most of our experiments, we also observed the color of the ocular fluids.

TECHNIC

In the course of the work, both adult and young dogs were used. The adult dogs were divided into groups 1 and 2. To those of group 1, toluylenediamine was given. The dogs were killed a number of days later, and the relation between the intensity of the jaundice in the blood serum and the color of the spinal and

* Submitted for publication, Dec. 9, 1929.

* From the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research, Chicago.

1 Roberts, M. H. Spinal Fluid in the New-Born, with Especial Reference to Intracranial Hemorrhage, *J. A. M. A.* **85**: 500 (Aug. 15) 1925, Intracranial Hemorrhage in the New-Born, *South. M. J.* **20**: 642, 1927, Relation of Pigment Content in Serum and Spinal Fluid of New-Born Infants, *ibid.* **21**: 460, 1928. Levinson, A., Greengard, J., and Lifvendahl, R. Cerebrospinal Fluid in the New-Born, *Am. J. Dis. Child.* **32**: 208 (Aug.) 1926.

2 Schmorl, G. Zur Kenntnis des Icterus Neonatorum, insbesondere der dabei vorkommenden Hirnveränderung, *Verhandl. d. deutsch. Gesellsch.* **6**: 109, 1903. For a discussion in English and other references to this subject see reference in footnote 10.

3 Personal communication to the authors from Dr. G. H. Whipple, of the University of Rochester Medical School.

ocular fluids was observed. The use of toluylenediamine for the purpose of producing jaundice was suggested principally by the work of Eppinger⁴

In these experiments, it was noted that the greatest degree of icterus occurred from two to four days after the administration of the toluylenediamine, and for this reason the spinal and ocular fluids were usually studied at this time.

In group 2 of the adult dogs, the common duct was first ligated and cut between the ligatures, and then, after a varying number of days, the toluylenediamine was administered as in the case of the dogs of group 1, and the same procedures followed. In one of these dogs, the cystic duct also was ligated.

The young dogs ranged in age from 6 to 8 weeks and were divided into three groups. In group 1, the common duct was ligated and cut between the ligatures, and after a number of days the relationship between the icterus index of the serum and the color of the spinal and ocular fluids was observed. To group 2, toluylenediamine only was administered. These dogs were killed a varying number of days later and studied as was group 1. To group 3, toluylenediamine was given a week after the common ducts were tied and cut. These were studied in the same manner.

The toluylenediamine was administered by stomach tube in the adult and by catheter in the young dogs. The dosages are recorded in tables 1 and 2. In the adult dogs, the drug was dissolved in about 30 cc of 70 per cent alcohol and then diluted to 150 cc with water. In the young dogs, the toluylenediamine was dissolved in 10 cc of 70 per cent alcohol and diluted with water to 60 cc.

The blood was drawn with a perfectly dry syringe and needle from a leg vein, in the case of the adult dogs, and by cardiac puncture in the case of the young dogs. The blood was centrifugated before clotting occurred, and the clot was then loosened and the blood again centrifugated. Clear, nonhemolyzed serum was always obtained. The icterus index in the case of the lighter-colored serums and of the cerebrospinal and ocular fluids was determined by the method of Brown⁵. In the case of the deeply jaundiced serums, the icterus index was determined by comparing the color of the serum in a known dilution with a physiologic solution of sodium chloride with 1/10,000 potassium dichromate in aqueous solution as a standard in a colorimeter. This standard solution has an icterus index of one⁶. The direct and indirect qualitative van den Bergh tests were made by the usual methods in all the serums and fluids⁷. The spinal and ocular fluids were also tested for hemoglobin by the benzidine tablet method of Roberts⁸. The dogs were killed by ether, and the spinal fluid was obtained by exposing the atlanto-occipital ligament, which was punctured by a 22-gage needle. This method

4 Eppinger, H, and Ranzi, E. *Die Hepato-Lienalen Erkrankungen*, Enzyklopadie der klinischen Medizin, Berlin, Julius Springer, 1920. Landa, E, and Starlinger, W. *Ueber den Einfluss der Toluylenediamine*, *Ztschr f d ges exper Med* **51** 213, 1926.

5 Brown, A. L. *A Rapid Clinical Method for the Determination of the Icterus Index*, *Arch Path* **3** 309 (March) 1927.

6 Maue, H. F. *Icterus Index of the Blood Serum*, *Surg Gynec Obst* **34** 752, 1922.

7 McNee, J. W. *Jaundice. A Review of Recent Work*, *Quart J Med* **16** 390, 1923. See footnote 10 for technic of van den Bergh tests on spinal fluid. The same technic was also used for the ocular fluids.

8 Roberts, D. *A Benzidine Tablet Test for Occult Blood*, *J A M A* **65** 244 (July 17) 1915.

ensured the obtaining of fluid free from traumatic blood. The aqueous humor was obtained by aspirating the anterior chamber of the eye with a 27-gage needle.

RESULTS

The results of the experiments are summarized in the accompanying tables. The icterus index of the blood serum of normal adult and young dogs is not stated in either of the tables. It was usually less than 1 and often 0, though it occasionally ranged between 1 and 2 in the older dogs. An icterus index of even 1 in dogs' serum is high,

TABLE 1—Results of Experiment to Produce Xanthochromia in Adult Dogs

	Gm Toluylene- diamine per Kg	Days Between Dosage with Toluylene- and With- drawal of Fluids	Icterus Index			Van den Aqueous Humor
			Blood Serum**	Spinal Fluid†	Aqueous Humor	
Group 1*						
Dog 1	0 03	4	15	0	§	§
Dog 2	0 04	10	80	0	§	§
Dog 3	0 10	3	169	0	§	§
Dog 4	0 10	2	182	0	0	0
Dog 5	0 10	4	(Dog dead)	1—†	0	0
Dog 6	0 03	3	182	§	§	§
		4	45	0	0	0
Dog 7	0 03	4	252	1—	1—	0
Group 2*						
Dog 8	0 03	3	370	1—	‡	0
Dog 9	0 05	5	150	1—	3	+
Dog 10	0 03	2	(Dog dead)	0	0	0
Dog 11	0 03	4	180	1—	4	+

* In group 1 the dogs received only toluylenediamine. In group 2 the dogs received toluylenediamine from three to five days after the common bile duct was tied and cut between the ligatures. The integrity of the ligatures was always checked by autopsy. In dog 11 the cystic duct was also ligated.

** Van den Bergh reaction positive in every case.

† Van den Bergh reaction negative in every case.

‡ 1—indicates icterus index less than 1.

§ This fluid was yellow, but the quantity obtained was insufficient for an accurate determination of the icterus index.

§ Not examined.

since dogs' serum is usually stated to be practically colorless⁹. Perhaps, the slight coloring of the serum in some of our dogs was due to some food factor, as the dogs had not been caused to fast before the beginning of the experiments and were on a mixed diet of milk, meat, bread and vegetables. The van den Bergh reactions of the normal serums were always negative. In group 1 of the adult dogs, the lowest icterus index of the blood serum at the time of obtaining spinal fluid was 15 and the highest 252. The spinal fluid was colorless in six cases, in two, it had a slight yellowish tinge. In one of the latter dogs, the icterus index of the blood serum was 252, the other dog was found

⁹ Van den Bergh, A. A. H., and Snapper, J. Die Farbstoff des Blutserums, Arch. f. klin. Med. **110** 540, 1913.

dead, and thus the icterus index of the blood serum could not be determined. The test for hemoglobin was negative in all the spinal fluids. The ocular humors were studied in four of these dogs, and there was a yellow tinge in the aqueous humor only in the dog the serum icterus index of which reached 252. Tests for hemoglobin made on the ocular fluids were negative. The van den Bergh reactions were negative in all the spinal and ocular fluids.

Whenever the van den Bergh test was positive in this work, both direct and indirect reactions were obtained, and thus throughout this paper no further reference is made as to whether the direct or indirect

TABLE 2—Results of Experiment to Produce Xanthochromia in Young Dogs

		Total Dose of Toluylene- diamine Mg	Days Between Dosage with Toluylene- diamine, and Withdrawal of Fluids	Icterus Index		
				Blood Serum†	Spinal Fluid†	Aqueous Humor†
Group 1*						
Dog	1	0	(Dog dead)	0	0	
Dog	2	0	10	0	0	
Dog	3	0	15	0	0	
Dog	4	0	8	0	0	
Group 2*						
Dog	5	40	4	8	0	
Dog	6	40	3	8	0	
Dog	7	20	2	28	1—	
Dog	8	40	3	9	0	
Dog	9	60	2	12	0	
Group 3*						
Dog	10	40	2	15	0	
Dog	11	40	5	(Dog dead)	0	
Dog	12	40	2	(Dog dead)	0	

* In group 1, the common bile duct was ligated and cut between the ligatures. No toluylenediamine was given. The blood, spinal and ocular fluids were examined from eighteen to twenty days after operation. In group 2, the dogs received only toluylenediamine. In group 3, toluylenediamine was given seven days after the common bile duct was ligated and cut between the ligatures.

† The van den Bergh test was positive in all the blood serums and negative in all the spinal and ocular fluids.

test was performed. The same holds true for negative van den Bergh tests.

In group 2 of the adult dogs, the highest icterus index of the blood serum was 370 and the lowest 150 at the time the blood was drawn. In the dogs of this group, a yellow tinge was present in the spinal fluid and aqueous humor in three instances. All these fluids failed to give a hemoglobin reaction. A positive van den Bergh test was obtained in two of the xanthochromatic aqueous humors, but in none of the spinal fluids. The icterus index of the yellow-tinged spinal fluid never even reached 1, but was as high as 3 and 4 in the aqueous humors which gave positive van den Bergh reactions. The vitreous was colorless in all cases.

In group 1 of the young dogs, the highest icterus index of the blood serum observed was 15, and no change was present in the spinal and ocular fluids. In group 3, the highest icterus index of the blood serum was also 15 and again the spinal and ocular fluids remained colorless. In group 2, the icterus index of the blood serum reached 28 in one dog, and in this case a yellowish tinge was present in both the spinal fluid and aqueous humor. Hemoglobin and van den Bergh tests were negative. No change occurred in the spinal and ocular fluids of the other young dogs of this group.

In the case of both adult and young dogs, complete autopsies were performed. Nuclear (kern) icterus did not occur in any instance.

COMMENT

The literature relating to the subject of icterus and xanthochromia in the spinal fluid has been reviewed by Glaser¹⁰. From it conflicting evidence is noted. Some investigators assert that bile pigments are present in all cases in the spinal fluid in jaundice. Others have found it in only a few cases, still others only in long-standing and severe jaundice. A few found no xanthochromia even in long-standing and severe jaundice. The icteric cases studied were usually of the obstructive type of jaundice with varying etiology. The ocular fluids were not mentioned in these papers.

In the work here reported there was a slight yellow tinge to the spinal fluid in five of the eleven adult dogs. The benzidine test for hemoglobin and the van den Bergh reaction for bile pigment were negative in every instance. The lowest icterus index of the blood serum in which there was an accompanying yellow cerebrospinal fluid was 150. The icterus index of the blood serum ranged as high as 182 without xanthochromia of the spinal fluid. This, perhaps, suggests a threshold for the appearance of xanthochromia under the conditions of our experiments. This is particularly probable since, with icterus indexes this high, owing to the difficulty of exactly matching yellow colors, a difference of 30 points may be within the limits of experimental error. The same general facts hold true for the aqueous humor, but with this fluid the xanthochromia became more intense than in the case of the spinal fluid and the van den Bergh reactions were positive. The vitreous humor remained colorless in all experiments.

The yellow aqueous humor occurring in these experiments suggests a possible explanation of xanthopsia in some cases of jaundice.

¹⁰ Glaser, J. The Cerebrospinal Fluid of Premature Infants, with Special Reference to Intracranial Hemorrhage and Pigmentation, *Am J Dis Child* **36**: 195 (Aug) 1928.

We were unable to produce any marked icterus in the young dogs comparable with that in the adult dogs. Toluylenediamine seemed to produce a severe anemia in the former without producing an intense jaundice. In one case in which the icterus index of the blood serum reached 28, there was a definite yellow tinge to both the spinal fluid and the aqueous humors, but the van den Bergh reactions in both fluids were negative.

The xanthochromia occurring in the spinal fluid of our dogs in the presence of negative van den Bergh reactions is probably due to the presence of bile pigment in insufficient amounts to give such a reaction, but sufficient to produce a faint yellow color. To determine whether this might be possible, we diluted some icteric dog serum with physiologic solution of sodium chloride until we reached a point at which a faint yellow color persisted, but the van den Bergh reaction was negative. The concentration of bilirubin in this solution was 1:1,650,000, if one considers that an icterus index of 100 roughly matches 100 mg of pure bilirubin per liter.¹¹ This dilution is thus just beyond the 1:1,500,000 dilution of pure bilirubin in which a positive van den Bergh reaction is still obtained.¹²

CONCLUSIONS

Xanthochromia may be produced in the cerebrospinal fluid and aqueous humor in experimental jaundice in dogs. Its appearance probably depends on the intensity of the icterus of the blood serum as measured quantitatively by the icterus index. Nuclear (kern) icterus was not produced.

In our experiments, the icterus index of the xanthochromatic spinal fluids never exceeded 1, the icterus index of the yellow aqueous humors ranged as high as 4. The vitreous humor always remained colorless.

The van den Bergh reactions were always negative in the xanthochromatic spinal fluids, but positive in the aqueous humors which had an icterus index of 3 or 4.

233 Oxford Street

11 Cutten, C., Emerson, E. E., and Woodruff, W. The Icterus Index, *Arch Int Med* **41** 428 (March) 1928.

12 Van den Bergh, A. A. H. *Der Gallenfarbstoff im Blute*, Leyden, S. C. van Doesburgh, 1918.

General Review

THE EVIDENCE FURNISHED BY BIOCHEMISTRY AND IMMUNOLOGY ON BIOLOGIC EVOLUTION ^

H. GIDEON WELLS, M.D.

CHICAGO

The story of the evolution of existing forms of life has been reconstructed almost entirely from anatomic evidence, of necessity, in respect to the evidence that has come from the fossils, and by tradition and inclination with most of the rest of it. In 1859, when Darwin put the subject of evolution on the front page of the daily papers and on all the pages of the religious journals, biologic science was mostly a matter of morphology and classification, as befits a young science. It was only in 1828 that Wohler had shattered the prevalent idea that organic substances must be the product of vital processes, simply by producing urea from ammonium cyanate. Pepsin had been discovered by Schwann only in 1836, and the digestive function of the pancreas had been revealed by Claude Bernard in 1846. These discoveries, together with that of the glycogenic function of the liver by Bernard, and Helmholtz' recognition of the muscles as the source of animal heat in 1848, had been large factors in giving rise to biologic chemistry as a separate division of physiology. Not until 1864 did Graham point out the fundamentals of colloidal chemistry. Organic chemistry had newly received its great stimulus in the production of aniline dyes from coal tar by Perkins in 1856. The "Cellular Pathology" of Virchow was only a puling infant of a few months' life. It was six years before Gregor Mendel announced the laws of heredity in a publication that was to be lost to the world until the same laws were rediscovered thirty-five years later. Physiology had not become sufficiently developed as a distinct field of science for the establishment of a Physiological Society of London until 1875, four years after Darwin's second great contribution, *The Descent of Man*, had been published.

Although evolution had been discussed, debated, and to some extent investigated even from "the Greeks to Darwin," as Osborn pointed out,

* Submitted for publication, Jan. 30, 1930.

^ From the Department of Pathology of the University of Chicago and the Otho S. A. Sprague Memorial Institute.

^ Tenth annual Pasteur lecture of the Institute of Medicine of Chicago, Nov. 22, 1929.

its birth as a major consideration in human thought was in 1859, in a cradle of science constructed almost solely of the branches of morphology, with coverings of systematization. Necessarily, the considerations of evolution in its early years were based on the evidence then available, which was almost exclusively structural, and because of this sort of environment in infancy its subsequent career has largely depended on morphologic contributions and considerations. This asymmetrical development is so marked that, as recently as 1926, Leathes in his presidential address to the Section on Physiology of the British Medical Association complained and asked "Why is it that what may be termed official physiology takes so little cognizance of the doctrine of evolution?" He suggested that possibly it was because these branches of biologic study followed courses so exactly parallel that they never met. And he pointed out that "natural selection applies to the survival of the chemical forms of living matter as it does to complex living organisms. These forms, infinitely protean in their variety survive and persist in so far and so long as they minister to self-regeneration. It is the principle of survival by service. Function alone gives permanence to structure." Therefore it is essential that function, with all that this involves, receive full consideration in working out the course of the evolution of the living world of today.

THE ORIGIN OF LIVING MATTER

Now, biologic function certainly depends even more on chemical properties than on anatomic organization. Formless enzymes may function actively, whereas the most elaborate anatomic structures in our museum jars function not at all, because their enzymes are dead. The evolution of life presumably had first to be the evolution of proteins, carbohydrates and fats, which then somehow constituted the living, probably at first formless, matter, and these were the important first steps in evolution. All the later strange divergencies into such elaborate creatures as cabbages and kings are matters of minor importance.

Therefore one turns to chemistry to see if it can offer a solution of the problem of the origin of life. Such explanations of the origin of life on the earth as that it is the result of the transportation of spores by meteors or star dust, even if true, are no solution, since they merely push back the origin of life to some other part of the universe. Presumably, one may suspect that the origin of life was the sequel of the formation of inorganic colloids, which served as the antecedents of the formation of organic colloids. It is generally agreed that life depends on the existence of organic colloids, partly because they form peculiarly labile compounds with crystalloids and water and perhaps

partly because, as I have elsewhere suggested,¹ colloids interfere greatly with the diffusion of other colloids and but little with the diffusion of crystalloids

Moore² speculated interestingly from the point of view of the biochemist on this matter of how life came to be. Recognizing the colloidal basis of life, he started it with the development of inorganic colloids, which could begin to form by aggregation of inorganic molecules when the materials of the primitive world had reached a temperature that permits such aggregates to exist

Moore said

The first primeval step would appear to be indicated by the union of single crystalloidal inorganic molecules to form inorganic colloids, and these metastable colloids acting on inorganic carbon compounds, such as carbon dioxide, in the presence of water and sunlight, and taking energy from the sunlight, built up at first simple organic bodies, and now these in turn reacting with one another formed more and more complex organic compounds. The fact that the present basis of the system of living creatures in the world is light energy leads to the view at a certain stage in the development of colloids, probably long before the appearance of chlorophyll, the colloids began to be affected by the light, and acquired the property of retaining and utilizing light energy for further development of structure, or, in other words, synthesis of more complex colloids. As the complexity of structure increased, the nature of the equilibrium in the colloidal aggregates would approximate more and more to that labile, easily destroyed, but also readily constructive condition which has been described as characteristic of all living things. In this manner we can conceive that the gulf between non-living and living things can be bridged over, and there awakens in our minds the novel conception of a kind of spontaneous generation of a different order from the old. The territory of this spontaneous production of life lies not at the level of bacteria or animalculae springing forth into life in dead organic matter, but at a level of life lying deeper than anything the microscope can reveal, and possessing a lower unit than the living cell, as we form our concept of it from the tissues of higher animals and plants

The evidence of geology clearly shows that life in some form appeared promptly when conditions of temperature made it possible, since the oldest sedimentary rocks show that already there were living forms that had much to do with the formation of these early strata of the world's crust. In the earliest of all stratified rocks, in the pre-Cambrian deposits of the Canadian Rockies, Walcott found fossilized structures that he interpreted as probably algae and bacteria, which were presumably an important factor in the deposition of these limestones before coralline structures had appeared in the world.

Moore reported that his experiments with a view to testing the synthetic action of sunlight in the presence of inorganic colloids (silicic

1 Wells, H. Gideon. *Chemical Pathology*, ed 2, Philadelphia, W. B. Saunders Company, 1914, p. 33

2 Moore, Benjamin. *Biochemistry, a Study of the Origin, Reactions and Equilibria of Living Matter*, London, Longmans, Green & Company, 1921

acid or colloidal uranium oxide) had shown it possible to observe the synthesis from CO_2 and H_2O , of formaldehyde (CH_2O), which is supposed to be the first step in the formation of carbohydrates, which are merely multiples of formaldehyde, e g, $6\text{CH}_2\text{O} = \text{C}_6\text{H}_{12}\text{O}_6$. Indeed, under the influence of light, formaldehyde polymerizes to produce substances which reduce copper solutions as do the carbohydrates. It is further possible for this formaldehyde in the presence of nitrates or nitrites to produce substances that can build up to form amino acids, and hence the fundamental steps in the evolution of carbohydrates and proteins are possible in the absence of living precursors—only carbon dioxide, water, nitrites and sunlight are necessary, and inorganic colloids are capable of speeding up the process.

It is interesting to note how close Lamarck came to this idea of the origin of life long before there was any knowledge of colloidal chemistry, for in 1802 he wrote

In the waters of the ancient world, and at the present time, very small masses of mucilaginous matter were collected. Under the influences of light, certain elements caloric and electric, entered these little bodies. These corpuscles became capable of taking in and exhaling gases, vital movements began, and thus an elemental plant or animal sprang into existence. Possibly higher forms of life, such as infest the intestines, originate in this way. Nature is thus always creating.³

If, as Moore suggested, life began by the development of formless colloidal complexes capable of accelerating synthesis under the influence of light rays, there still remains an unexplained wide gap between such hypothetical chemically active colloidal masses and the simplest microscopically visible living forms, the bacteria. Possibly, the invisible filtrable viruses represent an intermediate stage antecedent to the bacteria, but there is no knowledge as to how much real structure viruses have, or how many sorts there may be which cannot be recognized, because only those that produce disease make themselves known. It has even been suggested that the bacteriophages may be something like the genes that determine hereditary transmission of living characters, since they seem to be of approximately the same magnitude, that is close to 50 millimicrons in diameter.⁴

While such conceptions are at present purely speculative, they have enough reason in them even with the present scanty knowledge, to make it not fantastic that with more knowledge something like them may be found to be true. It is possible that one lives in a world of unknown, submicroscopic, little-organized living material, but the lack of observable chemical change in nutrient materials from which bacteria have been removed by filtration is against such a hypothesis.

³ Lamarck, quoted by Osborn. "From the Greeks to Darwin." New York, The Macmillan Company, 1908.

⁴ Alexander and Bridges. *Science* **70** 1821, 1929.

Presumably, the next stage in the evolution of life lies in those bacteria which can grow on inorganic mediums and synthesize their proteins, lipoids and carbohydrates from carbon dioxide and inorganic nitrogen, sulphur and phosphorus compounds. They secure their energy by oxidation of inorganic compounds, such as those containing the sulphhydryl and ferrous iron, and do not require organic compounds as a source of energy, therefore they can live and produce their own organic compounds without the aid of chlorophyll. And what seem to be fossil bacteria in the pre-Cambrian limestones have been described by Walcott.

The step from such synthesizing bacteria to the algae with chlorophyll was probably the next important phase in the actual creation of life as one now knows it, for only with the coming of chlorophyll to utilize the sun's energy did life on a large scale become possible. Hence the study of the nature and origin of chlorophyll may well give much information as to the steps by which the present living world was evolved. It certainly is of great significance that the oldest known geologic deposits that contain traces of living forms exhibit structures that seem to be algae, since even now the lowliest known organisms capable of synthesizing organic substances are the chlorophyll-containing algae. The bacteria with synthetic powers which can build up from inorganic materials their complex proteins and enzymes with all the properties of life, presumably preceded and evolved into the algae, but they could thrive only in the absence of direct sunlight which is fatal to them. Chlorophyll not only augments synthetic function, but by filtering off the ultraviolet rays enables life to go on despite the destructive action of sunlight.

THE EVOLUTION OF PROTEINS

Since the colloids characteristic of life have as their basic element the proteins, one of the most important of the first steps in evolution was the evolution of the amino acids that make up the proteins. Disregarding as not essential for the present the question of how the amino acids are linked together,⁵ one finds that in some mysterious way only a remarkably small number of the exceedingly great number of theoretically possible amino acids have been utilized to form the proteins. Only the amino acids with the amino group in the alpha position, next to the carboxyl group, seem to have been utilized, and of the vast number of possible alpha amino acids, only about a score have been needed to form all the kinds of proteins that go to make up the living world. Those most generally found are given in table 1.

⁵ Vickery and Osborne. A Review of Hypotheses of the Structure of Proteins, *Physiol Rev* 8 393, 1928.

TABLE 1—*Amino Acids Used in the Formation of the Proteins*^{*}

I MONO AMINO MONOCARBOXYLIC ACIDS	
1 Glycine	$\text{CH}_2\text{NH}_2 \cdot \text{COOH}$
2 Alanine	$\text{CH}_3 \text{CHNH}_2 \cdot \text{COOH}$
3 Valine	CH_3 $\text{>CH CHNH}_2 \cdot \text{COOH}$
4 Leucine	CH_3 $\text{>CH CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
5 Isoleucine	CH_3 $\text{CH}_2 \text{CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
II HYDROXY MONOAMINO MONOCARBOXYLIC ACID	
6 Serine	$\text{CH}_2\text{OH CHNH}_2 \cdot \text{COOH}$
III DIAMINO DICARBOXYLIC ACID CONTAINING SULPHUR	
7 Cystine	$\text{HOOC CHNH}_2 \text{CH}_2\text{—S—S—CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
IV MONO AMINO DICARBOXYLIC ACIDS	
8 Aspartic acid	$\text{HOOC CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
9 Glutamic acid	$\text{HOOC CH}_2 \text{CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
V DIAMINO MONOCARBOXYLIC ACID	
10 Lysine	$\text{NH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
VI DIAMINO MONOCARBOXYLIC ACID WITH GUANIDINE GROUP	
11 Arginine	$\text{HN} = \text{C} \begin{matrix} \text{NH}_2 \\ \text{NH} \end{matrix} \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
VII WITH BENZENE RING	
12 Phenylalanine	$\text{C}_6\text{H}_5 \text{CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
13 Tyrosine	$\text{HO C}_6\text{H}_4 \text{CH}_2 \text{CHNH}_2 \cdot \text{COOH}$
VIII WITH INDOLE RING	
14 Tryptophan	C_6H_4 $\begin{matrix} \text{C—CH}_2 \text{CHNH}_2 \cdot \text{COOH} \\ \diagup \quad \diagdown \\ \text{CH} \\ \diagdown \quad \diagup \\ \text{NH} \end{matrix}$
IX WITH PYRROLE RING	
15 Proline	$\begin{matrix} \text{CH}_2\text{—CH}_2 \\ \quad \\ \text{CH}_2 \quad \text{CH COOH} \\ \diagup \quad \diagdown \\ \text{N} \\ \\ \text{H} \end{matrix}$
16 Oxypoline	$\begin{matrix} \text{HO CH—CH}_2 \\ \quad \\ \text{CH}_2 \quad \text{CH COOH} \\ \diagup \quad \diagdown \\ \text{N} \\ \\ \text{H} \end{matrix}$
X WITH IMIDAZOLE RING	
17 Histidine	$\begin{matrix} \text{CH} \\ \diagup \quad \diagdown \\ \text{N} \quad \text{NH} \\ \quad \\ \text{CH} = \text{C—CH}_2 \text{CHNH}_2 \cdot \text{COOH} \end{matrix}$

^{*} From Kennaway Notes on the Evolution of Proteins, Chem News 13 120, 1920

On scanning the list in table 1, one sees at once that these nowhere form a complete series. For example, if there is one hydroxy acid (serine) corresponding to alanine, why should there not be found the hydroxy derivatives of all the other amino acids? And why but one sulphur-containing amino acid, and but two dicarboxylic acids, and three diamino acids, and three with the benzene ring, when apparently it would be just as easy to form many more? Presumably, vastly more than these few sorts of amino acids have occurred in nature, yet for some reason they have been discarded as unsuitable or unnecessary for the sorts of proteins that are required to make a living organism. Nor are all the few known amino acids of proteins necessary for each and every protein, for no protein yet analyzed has been found to contain all of them, and many proteins seem to contain relatively few. It is perhaps significant that the proteins most concerned with cell multiplication and heredity, the nucleoproteins of the germ cells, seem to have the smallest number of different amino acids, as if these few amino acids were the essential ones to keep life going and reproducing, while the rest represent merely those responsible for the differentiation and the functions less essential than reproduction.

The possible number of isomeres of an organic compound depends on the number of asymmetrical carbon atoms, hence proteins, formed of linked amino acids, most of which contain such asymmetrical carbon atoms, possess exceptional possibilities for chemical differentiation. As Lillie⁶ emphasized, "The specific characters of any animal or plant are determined ultimately by the specific characters of its structure-forming proteins. The developing germ or growing organism synthesizes specific proteins, and these, since they determine the structural and hence the physiological peculiarities of the organism, form the basis of its special character as an organic species."

As to the possibilities for variation present in the composition of proteins made up of such a limited number of amino acids to account for the vast numbers of known and unknown, living and extinct forms of life, this statement may be taken from Leathes

Supposing it were a chain of only fifty links, a very simple case, if all the links were different the number of possible permutations is denoted by the innocent-looking symbol $|50|$. If, instead of all being different, one kind of link recurred ten times, the number would be reduced to $|50/10|$. If, in addition, there were four that recurred four times and ten recurred twice, it would be further reduced to

$$|50/10| \times (4)^4 \times (2)^{10}$$

It would now consist of a chain of only fifty links, of which there were only nineteen different kinds, and the number of different arrangements of its parts would

6 Lillie, Ralph. Biol. Bull. **34** 65, 1918

be about 10^{48} Astronomy deals with big figures Light, it is said, takes 300,000 years to travel from one end of the Milky Way to the other, this distance expressed in Angstrom units, 10,000,000 of which go to a millimeter, would be less than 10^{32} So far are we from knowing the structure of protein molecules So far are we from knowing what variations in disposition of the parts in such a molecule may not occur without our being within a measurable distance of detecting them For if the number of possible varieties of a protein whose molecular weight is known, and known to be exceptionally small, and which contains the several amino acids in a known proportion, is as great as this, the number that is possible when that proportion may be changed is practically incalculable, each change in proportion being capable of a number of new arrangements that could be calculated, as was done for our hypothetical case

It is most significant, furthermore, that much the same amino acids are found in all living cells, whether they be simple bacteria and yeasts, or the vastly more complex plants and animals As Kennaway said of these analytic results

They show that the simplest organisms now existing do not contain a series of amino-acids any more primitive than that present in the higher organisms One may suppose that the present apparently stereotyped series of utilisable amino-acids represents the stable outcome of a struggle long ago among simple organisms in which those which made a less suitable choice were beaten, and have passed away leaving no trace We cannot know the biochemistry of the first organisms which appeared upon the earth, the experiments and discarded compounds of that time are lost The selection of amino-acids must have taken place at an immensely remote period, for the earliest records which we have of the forms of life on the earth do not show us organisms which have any appearance of noteworthy difference in chemical composition from those which exist at the present day Thus one of the earliest fossils, the brachiopod *Lingula* of the Cambrian period, is very closely related to a species now living Structures regarded as fossil Algae very similar to recent species have been found in still older rocks The doctrine of natural selection gives the impression that evolution proceeds throughout in a very gradual manner But at the time when the amino-acids were first being produced and tested, organic evolution must have proceeded very distinctly *per saltum* as each new compound was synthesized, natural selection would then act slowly and surely upon the organisms which made one or another choice, and thus the present series of amino-acids was delimited

In view of the general principle that the individual in its development tends to recapitulate the development of its species, one might hope to find the various steps of the evolution of the protein in the substances produced when bacteria or yeasts synthesize their own proteins from the simple mixtures of salts that they are able to utilize in reproducing themselves in vast numbers But unfortunately this is not the case The reproduction is completed so rapidly that one cannot catch the different stages This is indeed a marvelous feat, and Kennaway said

In the time taken by a yeast cell to produce another by budding, when growing on a medium such as Pasteur's containing no nitrogen but that of ammonium tartrate, it must synthesise each one of the amino-acids present in the yeast cell,

and combine them as a series of polypeptides until its proteins are produced, and all the while carry on many other chemical operations. Even when one takes into account the small size of molecules it is wonderful that so many reactions can be kept apart within the compass of a yeast cell.

CHEMICAL STEPS IN EVOLUTION

One cannot hope, therefore, to learn through chemical analysis of growing cells the steps by which the proteins as they exist now were evolved. Even chemical study of that beautiful material for the investigation of the evolution of the individual, the developing eggs of hens, has not as yet thrown any light on the problems of evolution, although there is room for much more profitable study in this field.⁷ As Needham pointed out, the developing egg is a closed system, without the usual complications for the biochemist of intake, excretion and bacteria. From a small variety of proteins, carbohydrates and fats, are formed in a few days the vast variety of components of the mature chick. From morphologic studies of the developing chick, much has been learned about the evolution of structure. Undoubtedly, closer biochemic study of developing eggs would give evidence as to the evolution of chemical structures. The vitally important nucleic acids, with their purines and pyrimidines which form so large a part of the hatching chick, are almost entirely new-formed from other components during incubation. What are the steps of evolution of purines and nucleic acids? Can one not learn the chemical evolution of keratin, as well as one knows the morphologic evolution of birds' feathers from fishes' scales? If one could follow the transformations that produce hemoglobin in the egg, one would probably learn how it came into existence in the Cambrian. And one might follow the development of enzymes as well. Needham, who is one of the few biochemists attacking the problem of the evolutionary significance of the changes in the developing egg, brought out an interesting bit of evidence of the well known relationships of birds and cold blooded forms by showing that the developing chick and dogfish embryos alike have to synthesize 90 per cent of the scyllitol that they produce.⁸ There is, furthermore, the suggestive discussion of the "Paleochemistry of Body Fluids and Tissues" by Macallum⁹ suggesting that the inorganic constituents of one's body portray the composition of the pre-Cambrian seas from which one's ancestors arose.

That important functions may not come until late in the development of the egg is well illustrated by the observation of Murphy¹⁰ of the

⁷ Needham, J. The Metabolism of the Developing Egg, *Physiol Rev* **5** 1, 1925

⁸ Needham. *Biochem J* **23** 319, 1929

⁹ Macallum, A. B. *Physiol Rev* **6** 316, 1926

¹⁰ Murphy. *J Exper Med* **19** 181, 1914

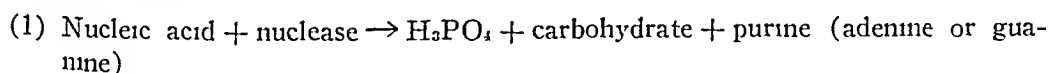
Rockefeller Institute, that in the early days of development of the chick it offers no resistance to the implantation of foreign tumor cells, even mammalian tumor cells. Only after the eighteenth or nineteenth day of incubation does the chick acquire the capacity to destroy the foreign cells, which it does suddenly and effectually. Even after that stage of its evolution, the chick is able to prevent mammalian tumor cells from living in its tissues.

Undoubtedly, biochemistry can give more than it so far has to establishing relationships and distinctions between different animal forms, to supplement or to test the evidence that has been furnished by anatomic studies. For example, anatomic studies have shown that the central nervous system is derived from the same cells as those which produce the surface epithelium. In accord with this, biochemists have found that the central nervous system contains a form of keratin, neurokeratin, which seems to be chemically like the keratin which characterizes the surface epithelium. And forty years ago, Kuhne and Chittenden¹¹ showed that such species as lobsters, which have chitin for an exterior covering instead of keratin, also have neurochitin instead of neurokeratin in their nervous tissues.

How much heredity and evolution are matters of chemistry and enzymes is apparent when one considers how much weight one gives to the color of the coat in establishing the relationships of animals, whether one is observing the furs of quadrupeds, the feathers of birds or the skin of man. For these colors mostly depend on the amount of melanin formed from aromatic compounds by the action of oxidizing enzymes, and the characteristically inherited character of albinism depends apparently on an absence of the proper enzyme in some cases, and in others on the presence of a specific inhibitor of the enzyme (Onslow)¹²

EVOLUTION OF THE PURINE ENZYMES

The story of the enzymes of purine metabolism¹³ is a beautiful example of the possible unearthing of biochemical evidence in respect to evolutionary history. The steps by which the complex nucleoprotein molecule is broken down by several different specific enzymes is something like this¹⁴



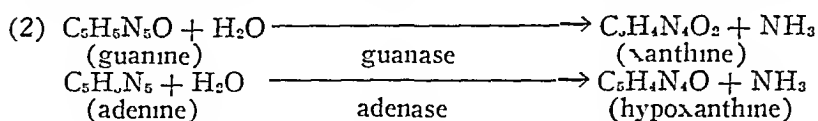
¹¹ Kuhne and Chittenden. *Ztschr f Biol* **26** 291, 1890

¹² Onslow. *Proc Royal Soc London (B)* **89** 36, 1915. Marinesco. *Rev Sc* **60** 321, 1922

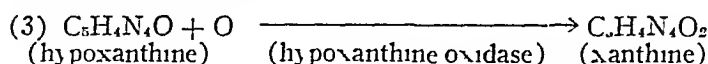
¹³ Wells, H. Gideon. *Some Features of Purine Metabolism*, *J Lab & Clin Med* **1** 164, 1915, *Chemical Pathology*, ed 5, Philadelphia, W. B. Saunders Company, 1925, chap 25

¹⁴ For simplicity the various different lines of cleavage in the disintegration of nucleic acid are not considered separately

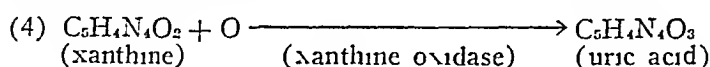
These two purines are then attacked by specific deaminizing enzymes, guanase or adenase, as shown in the following matter



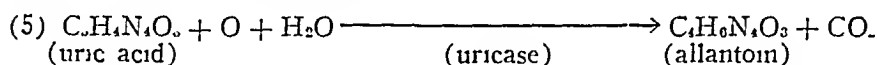
The hypoxanthine formed from adenine is then oxidized by a specific enzyme to xanthine



Then the xanthine which has been derived in this way from both adenine and guanine is oxidized to uric acid



And lastly, in many species of animals the uric acid is further oxidized to the more soluble allantoin



It is thus evident that the steps of the disintegration of nucleic acid are numerous, but that each separate process is a simple one, and also, that it has been possible to follow out and distinguish the several steps and to establish the fact that each step depends on a distinct and specific enzyme. Not only has all this work been accomplished, especially by Walter Jones and his associates, but, furthermore, these several enzymes have been studied in many different species and tissues, and found to have a most peculiar and characteristic distribution. Not every tissue possesses all the enzymes of purine destruction, and in different species of animals the distribution of the enzymes is different. For example, the enzyme xanthine-oxidase, which oxidizes xanthine into uric acid, is found in man only in the liver, and in other animals it is also of limited distribution, being found usually only in the liver or in the liver and the kidneys, but in the dog it seems to be present in several tissues. The deaminizing enzymes, adenase and guanase, are much more widely distributed, but by no means universally. Adenase, for example, is not present in the tissues of the rat or those of adult human beings. Guanase is absent from the spleen and the liver of the pig and from human spleen, although present in most other tissues. Uricase, the enzyme which destroys uric acid, also has peculiarities of distribution, being seldom found in any tissue other than the liver or the kidney, and being absent entirely from the tissues of man and from the birds and reptiles so far examined. The significance of this distribution of uricase will be discussed at greater length a little later.

Now, while it is unquestionably true that the results of laboratory experiments with tissue extracts cannot always be used literally in the elucidation of metabolism in living animals, yet it has developed that the results thus obtained with purine enzymes fit remarkably well with results of studies of metabolism, so that they are entitled to consideration and confidence. For example, the absence of uricase in man, birds and reptiles agrees perfectly with the fact that in the same animals one finds much excretion of unchanged uric acid, whereas in all those animals that excrete little or no uric acid and much allantoin, we find the enzyme uricase. Furthermore, a striking correspondence is found in the absence of guanase from the liver and the spleen of the pig and the occurrence of a form of gout in pigs with deposition of guanine rather than of uric acid in the tissues.

In connection with this discussion of the biochemical evidence on evolution, there are certain interesting observations on the general biologic features of the purine enzymes. One is that these enzymes appear one by one in the development of the individual, and that the order of their appearance is correlated, in general, with their distribution in the ascending scale of animal evolution. To illustrate—in the developing pig it was found by Mendel and Mitchell that only nuclease is present in the earliest stages, adenase appears by the time the fetus has reached a length of 50 mm, but xanthine oxidase appears only at about the time of birth, while uricase appears somewhat later. So, too, in the human fetus, guanase is present by the third month, but xanthine oxidase does not appear until at or near full term, and uricase never develops.

If one compares these observations with the occurrence of these same enzymes in organisms of varying stages of development in the biologic scale one finds a correlation that must be more than fortuitous. Thus, in a unicellular organism (yeast) there are found only nuclease, which seems to be present in all living cells, and guanase, this corresponds to the early human or pig embryo, each with nuclease and one deaminizing enzyme. A mollusk (*Sycotypus canaliculatus*) was found to contain nuclease and both deaminases, corresponding to a later stage of mammalian development. The reptiles and birds are in the same stage of development as the mature human or pig fetus, being equipped with nuclease, adenase, guanase and xanthine oxidase, but unable to destroy uric acid because of a lack of uricase. Uricase seems to be a late development, acquired chiefly by mammals, and not by all of them. On the basis of the facts cited, and supported by others not mentioned, one may say that in the formation of purine enzymes one has an apparent exemplification of the biologic law that the individual in its development tends to recapitulate the development of its species—"ontogeny recapitulates phylogeny."

Our studies¹⁵ on the occurrence of purine enzymes in tumors also gave interesting results in general harmony with the statements made in the preceding paragraphs, for it was found that benign tumors tend to have the full equipment of enzymes of adult tissues, while malignant tumors are likely to lack the enzymes that appear latest, and thus exhibit their embryonic character chemically, just as they do under the microscope

As pointed out, uricase, the enzyme that oxidizes uric acid to allantoin, is a late development in the mammals, and in them not formed until the time of birth. While present in nearly all mammals so far examined, it is interesting to learn that the chief exception is formed by man and his closest relations, the higher anthropoids. All the common domestic and laboratory animals that have been examined, including a marsupial, the opossum, destroy most of the uric acid formed in their metabolism and excrete it as allantoin. It is always possible to demonstrate the presence of uricase in the tissues of these animals. Even different species of monkeys are likewise endowed with uricase, but not the orang-utans and chimpanzees that we have examined. Hence these two anthropoid apes (and presumably the gorilla, which has not been studied) stand together with man apart from all other animals in their deficiency in uricolytic enzymes. It is of particular interest that we find here that the anthropoids resemble man, while the monkeys resemble the lower mammals, since this observation furnishes a chemical corroboration of other biologic facts indicating that the anthropoid apes are more closely related to man than to the monkeys. And it is a striking fact that in this particular respect man and the anthropoid apes are less highly developed than other mammals, for, as pointed out previously, the uricase is a late development in the animals that possess it, and apparently is the last acquisition in purine metabolism in the course of the development of many lines in the animal kingdom. Presumably, it is this lack of uricase to destroy uric acid that accounts for the existence of gout as a human disease, for birds, also lacking uric acid, readily get gouty deposits, and swine, which lack guanase to destroy guanine, suffer from a form of gout with deposits of guanine.

As far as purine metabolism is concerned, man and the anthropoid apes rank in development with birds, reptiles and some mammalian fetuses at about full term. But amphibians and some fish (selachians) can oxidize uric acid,¹⁶ although the bony fish (teleosts) cannot do so. The amphibians, indeed, go even farther than the mammals, for they destroy the allantoin.

15 Wells and Long. *Ztschr f Krebsforsch* **12** 598, 1913. Long. *J Exper Med* **18** 512, 1913.

16 Przylecki. *Arch internat physiol* **26** 33, 1926.

An interesting analogy is observed in respect to the fatty acid metabolism of man and the anthropoids, for, as pointed out by Friedemann,^{16a} among the mammals so far investigated, only man and the apes seem to develop ketosis with excretion of aceto-acetic and β -hydroxybutyric acid on fasting. Apparently, the other mammals possess some sort of ketolytic mechanism not possessed by man and the anthropoid apes, whereby they are protected from the ketosis from which man and the apes often suffer.

In these respects, as well as many others, man is far from being the most highly developed of the mammals. One is too accustomed to assume complacently that man represents the apex and consummation of evolution. As a matter of fact, he occupies in many respects merely an intermediate position among the mammals, and excels only because of the superior development of his central nervous system, much aided by the lack of specialization of his upper extremity. Newman said that this is among the most primitive limbs of any of the land mammals. It is not modified for any single function, but remains generalized and therefore a versatile tool of the brain. Undoubtedly, man would be much better off and immune to gout if he had acquired the power possessed by nearly all other mammals, of converting uric acid into the vastly more soluble allantoin. And he must stand humbled before the more talented frog, which can also convert the allantoin into urea. It is safe to assume that frogs do not have gout. Needham¹⁷ evolved a most entertaining theory of why birds and reptiles excrete uric acid, which time and space will not permit me to discuss as fully as I am tempted to do. Briefly, the idea is that in terrestrial oviparous animals the amount of water available for the excretion of the nitrogenous waste of the embryo into the closed system formed by the egg shell is so limited that only a precipitable nitrogenous substance, such as uric acid, can be gotten rid of without its diffusing back into the embryo. The chick embryo possesses uricase up to the sixth day, and in that period excretes urea and ammonia, recapitulating its aquatic ancestry chemically as it does anatomically with its gill clefts. "When the reptiles came ashore they found it was as well to leave their uricase behind them." But as uric acid is an extravagant excretion product, wasting more carbon and oxygen than urea and ammonia, it seems to have been utilized chiefly by those species in which it serves a purpose in the developmental stages—man and the anthropoids being an unexplained exception.

There is a remarkable, almost amusing, exception to the statement that all mammals except man and the higher apes oxidize uric acid to allantoin before excreting it, for the exception is the black and white

^{16a} Friedemann *Science* **67** 221, 1928

¹⁷ Needham, J *Science Progress* **23** 633, 1929

spotted coach hound, the dalmatian, that used to trot behind those vehicles that were "classy" enough to be called equipages. It has become almost extinct since gasoline superseded oats as a motive power. Benedict stumbled on the fact that unlike every other sort of dog, pedigree or mongrel, that any one has examined, the dalmatian excretes large amounts of uric acid, but also much more allantoin than does man. The latter fact indicates that it is not entirely devoid of uricolytic power, and the liver of one dalmatian that I studied showed the presence of uricase.¹⁸

Breeding of dalmatians with other dogs has produced hybrids which Onslow¹⁹ found to show a segregation of the character involving the power to destroy uric acid from the character involving lack of this property. In the first hybrid generation, the excretion of uric acid was low and that of allantoin high, as in normal dogs, but in the second hybrid generation one of five dogs excreted much uric acid, as does its dalmatian grandparent. Evidently, then, this reduced ability of the dalmatian coach hound to oxidize uric acid is a recessive character. Perhaps this may be looked on as a biochemical illustration of a genetic mutation.

This story of the stepwise development of the enzymes of purine metabolism fits well with the hypothesis that ontogenetic evolution may depend on a series of enzymes within the cells which become active in fixed succession and thus determine the morphologic and physiologic properties gradually manifested in the development.²⁰ This and related lines of thought have become the basis of systematic investigations, especially by Goldschmidt,²¹ and von Euler and his associates,²² who report that they have shown the dependence of certain mendelian manifestations of heredity in barley on the distribution of enzymes in the chromosomes.

HEMOGLOBIN CRYSTALS AS EVIDENCE OF EVOLUTIONARY RELATIONSHIP

It is apparent that the contributions of biochemistry to the story of evolution are waiting on more knowledge and better methods, for one finds that the most suggestive items have been provided by the

18 Wells, H. Gideon. The Purine Metabolism of the Dalmatian Coach Hound, *J Biol Chem* **35** 221, 1918.

19 Onslow. *Biochem J* **17** 334 and 564, 1923.

20 Beijerinck. *Proc koninkl Akad Wetenschappen, Amsterdam* **19** 1275, 1917.

21 Goldschmidt, R. *Quart Rev Biol* **3** 307, 1928. Guyer. *Science* **71** 169, 1930.

22 Von Euler, H., Hellstrom, H., and Runehjelm, D. *Ztschr f physiol Chem* **182** 205, 1929, **185** 74, 1929.

use of the most delicate methods for differentiation of proteins—crystallography and immunology. Unfortunately for biochemistry, the crystallization of proteins is difficult, and with most of them impossible. The studies of Reichert and Brown²³ on proteins that do crystallize, the hemoglobins, show what can be done by the exact methods of crystallography. These disclose that even with such a substance as hemoglobin, which, having a common function in all species, might be expected to be much the same in all species, recognizable differences do occur. Although the constant recurrence of certain angles in the hemoglobins of various species, even when the species are widely separated and the crystals belong to various crystal systems, indicates a common structure of the hemoglobin molecules, whatever their source, nevertheless constant differences are present which distinguish one species from another.

For example, Reichert²⁴ said

When orders, families, genera or species are well separated the hemoglobins are correspondingly markedly differentiated. For instance, so different are the hemoglobins of *Aves*, *Marsupialia*, *Ungulata* and *Rodentia* that there would be no more likelihood of confounding the hemoglobins than there would be of mistaking the animals themselves. Even where there is much less zoological separation, as in the case of the genera of a given family, but where there is well-marked zoological distinction, the hemoglobins are so different as to permit readily of positive diagnosis. When, however, the relationships are close the hemoglobins are correspondingly close, so that in instances of an alliance such as in *Canis*, *Vulpes* and *Urocyon*, which genera years ago were included in one genus (and doubtless correctly) the hemoglobins are very much alike, and in these cases they may exhibit closer resemblances than may be found in general in specimens obtained from well-separated species of a genus.

So distinctive zoologically are these modified forms of hemoglobins that we had no difficulty in recognizing that the common white rat is the albino of *Mus norvegicus* (*Mus norvegicus albus* Hatai) and not of *Mus rattus*, as almost universally stated, and that *Urisidae* are related to *Phocidae* (as suggested by Mivart thirty years ago), but not to *Canidae*, as stated in modern works on zoology. Moreover, we were quick to detect errors in labeling, as, for instance, when a specimen marked as coming from a species of *Papio* was found to belong to one of the *Felidae*. Generic forms of hemoglobin when obtained from well-separated genera are, in fact, so different in their molecular structures that when any two are together in solution they do not fuse to form a single kind of hemoglobin or a homogeneous solution, but continue as discrete disunited particles, so that when crystallization occurs each crystallizes independently of the other and without modification other than that which is dependent upon such incidental conditions as are to be taken into account ordinarily during crystallization. Thus, the hemoglobin of the dog crystallizes in rhombic prisms which have a diamond-shaped cross-section, that of the guinea-pig in tetrahedra, that of the squirrel in hexagonal plates, and that of the rat in elongated six-sided plates. When any two of these

²³ Reichert, E. T., and Brown, A. P. The Crystallography of Hemoglobins, Publication 116, Carnegie Institution of Washington, D. C., 1909.

²⁴ Reichert. Science 40 649, 1914.

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hemoglobins are together in solution and crystallization occurs, each appears in its own form. Such phenomena indicate that the structures of the hemoglobin molecules are quite different, in fact, more differentiated than the molecules of members of an isomorphous group of simple carbonates, such as the carbonates of calcium and magnesium which when in separate solutions crystallize in rhombohedrons whose corresponding angles differ $2^{\circ} 15'$, but which when in molecular union, as in the mineral dolomite, crystallize as a single substance which has an intermediate angle.

Upon the basis of our data it is not going too far to assume that it has been satisfactorily demonstrated theoretically, inferentially and experimentally that at least this one substance (hemoglobin) may exist in an inconceivable number of stereoisomeric forms, each form being peculiar to at least genus and species and so decidedly differentiated as to render the hemoglobin crystal test more sensitive in the recognition of animals and animal relationships than the zooprecipitin test.

Subsequent to the research referred to, investigations have been pursued in the study of hemoglobins from various additional sources, especially from representatives of *Primates*, with the result in the latter case of finding indubitable evidence of an ancestral alliance of man and the manlike apes.

Such studies as those of Reichert and Brown are valuable as affording a new and exceedingly delicate means of establishing differences and relationships between various hemoglobin-possessing forms, and somewhat similar methods serve to differentiate between starches.²⁵ The results so far obtained have largely served to establish the fact that the classifications that have been set up in the plant and animal kingdoms on the basis of morphology are well justified by these chemical studies. It is probable that these methods may serve to settle disputed points of relationship, as in the case of the albino rat, and perhaps will lead to some readjustment of existing classifications. But on the whole one must admire the accuracy with which the morphologists have done their systematization, and marvel at the fact that morphologic differentiation corresponds with, and presumably depends on, chemical differences. Of course there are found discrepancies between the structural and the chemical relationships. As Newman²⁶ said

For that matter there is no parallelism between classifications based on teeth and that based on feet, or between any two other unconnected systems. No two systems of an organism exactly keep pace in evolution. One may remain relatively conservative, while another undergoes pronounced specialization. Of all systems the blood seems to be the most conservative and to have retained longest its ancestral condition. It is on this account that blood tests so often reveal relationships that can scarcely be revealed in any other way.

²⁵ Carnegie Institution of Washington, D. C., publication 173, rev., *Am. J. Botany* 3: 91, 1916.

²⁶ Newman, H. H. *The Gist of Evolution*, New York, The Macmillan Company, 1926.

IMMUNOLOGIC EVIDENCE

Of even wider applicability, since they require no crystallization or other physical constants, are the methods of immunology, which itself constitutes one of the most important of the branches of biochemistry²⁷ The serologic reactions are essentially delicate methods for differentiation of proteins (either alone or as the complexes existing in protoplasm), and since the evolution of different species is essentially the evolution of different combinations of amino-acids to form the proteins characteristic of each species, and the carbohydrate and fatty compounds that help them to make up cells, evidently the serologic reactions afford a means for the analysis of the evolutionary relationship of species

This opportunity was recognized in the earliest days of immunology by that pioneer in the study of the precipitin reaction, George H F Nuttall of Cambridge University The precipitins were first studied in 1897 by Kraus, and in 1904 Nuttall²⁸ published his monograph in which he recorded 16,000 precipitin tests made with the blood of a vast range of animal species This pioneer work of Nuttall's blazed a broad trail which, for some unknown reason, has been little followed Since that time methods have been improved, so that much more clear distinctions and more quantitative results are obtainable, yet few applications of these methods have been made to problems of zoological and botanic differential classifications

In general, the results obtained by Nuttall were in accordance with the statement made previously, that the existing morphologic classification corresponds well with the chemical differentiation For example, antiserum for the blood of domestic cats gave the strongest reaction with the blood of cats, weak reactions with other carnivora, and none at all with the blood of primates, ungulates and marsupials Antidog serum gave a stronger reaction with the blood of jackals than with blood from less closely related carnivora Antipig serum gave no significant reactions with the blood of many other mammals, including whale blood, despite the tradition of some relationship between these two dissimilar mammals Antillama serum showed the relationship of this animal to the camels Antimarsupial serum established the relationship of several members of this group, and the lack of relationship to other mammals Antiserum for the blood of fowls and ostriches showed a general relationship of the serum of many kinds of birds, a slight relation to reptiles and almost complete distinction from the mam-

27 Wells, H Gideon Immunology as a Branch of Chemistry, New York, Columbia University Press, 1927

28 Nuttall, G H F Blood Immunity and Blood Relationships, London, Cambridge University Press, 1904

mals So too, antisera for blood and egg proteins showed strong relationships between turtles, alligators and crocodiles, and a slight but distinct relationship of these reptiles with the birds, corroborating the paleontologic evidence of the origin of the birds from the reptiles. Antiserum for lobster blood reacted only with the blood from decapods. An interesting result was obtained by Graham-Smith with antisera for *Crustacea* and for the king-crab, *Limulus*, for it was found that the limulus, famous as a "living fossil" because it has come down almost unchanged for so long a geologic history, is not related to the crab at all, but to the spiders—a conclusion that had also been advanced on anatomic grounds.

This work was done by relatively crude methods that did not permit the establishment of the minor degrees of relationship and distinction that are possible by methods now available, and there is no doubt that much more valuable evidence is to be obtained by any one who again ventures into the field with refined methods. For example, several investigators have found that immunologic comparisons of the blood of rats and that of mice shows them to be much less closely related than their general similarity of appearance and habits would indicate.²⁹ And Kritchevsky³⁰ has adduced by the method of complement fixation some evidence that the embryonic frog in the tailed tadpole state is intermediate between the frog and the tailed amphibian *Triton*, which may be looked on as a precursor of tailless amphibians.

The limited studies of quantitative relations with the precipitin reaction by Boyden,³¹ as far as they went, in general confirm Nuttall's observations, and Boyden's conclusion is that "the degree of reaction between an antiserum and various animal bloods has in general paralleled the relationship between those animals. Thus nearly always the reaction of a given antiserum is greater with animals belonging to the same order than with members of other orders." He emphasized the desirability of applying immunologic methods to the zoologist's problems in respect to the relationship of the animals now in dispute.

It must be admitted that the results of phylogenic studies as yet obtained by means of simple immunologic tests do not contradict the conclusion of Erhardt³² that, although useful for such studies serologic methods are less valuable than the anatomic comparisons. But the possibilities of such investigations have been enhanced by recent investigations on specificity especially those of Landsteiner which have

29 Steffenhagen and Schoenburg. *Ztschr f Immunitätsforsch u exper Therap* 8 563, 1911

30 Kritchevsky. *Centralbl f Bakteriöl* 72 81, 1914

31 Boyden. *Biol Bull* 50 73, 1926

32 Erhardt. *Ztschr f Immunitätsforsch u exper Therap* 60 156, 1929

brought out the fact that animals possess two sorts of specific substances, simple proteins and complex antigens, the latter of which are proteins combined with other substances, especially lipoids Landsteiner³³ said

Aside from the chemical study of antigens it was noticed that the specificity of the serologic reaction of blood cells obeys other rules than does the species specificity of proteins as shown by precipitin reactions. This led to the conclusion that there exists a two-fold system of species specificity in animals. In the case of the proteins, the serological and chemical properties in general parallel closely the zoological relationship and the changes are gradual (Nuttall, Reichert, and Brown). Thus one could roughly construct the zoological tree merely on the basis of precipitin reactions. The specificity of cells is characterized on the contrary by the occurrence of so-called heterogenetic reactions which disclose the existence of similar structures in unrelated species and at a glance would indicate a mosaic structure.

A second distinguishing feature is the fact that allied species as a rule can be differentiated by hemagglutinins but not by precipitins. This is hardly caused by the unequal sensitivity of the two methods only, because with erythrocytes the said differences are considerable in comparison with those exhibited by distant species.

That individual protein differences occur has been assumed also on the basis of purely chemical investigations. Meyer and Treudtel found differences in the flocculability and the isoelectric point of casein prepared from the milk of various women. The existence of more than one form of hemoglobin in the blood of one species was reported by Kuster and by Anson, Barcroft, Mirsky and Oumuma. According to the claims of Falkenhausen and Fuchs, racial differences in proteins can be detected by the action of digestive serum ferments. It will be of importance to repeat and extend these studies and to ascertain whether the findings bespeak constitutional and hereditary variations of proteins among individuals, analogous to those which have been found to exist in the complex cell antigens or their haptens. If the answer is in the affirmative one should rather expect to obtain parallel results by serological reactions.

Since species are characterized not only by morphological attributes but by their specific biochemical constitution as well, it seems evident that the somatic and functional development of the organic world was paralleled by a biochemical evolution of the proteins and haptens. One must assume that the two lines of events are linked in some way, although no explanation has been offered as to how such a correlation might be brought about. In this regard it is essential to know whether the small initial steps in evolution are coupled with changes in the proteins. If so, individual and racial protein differences, perhaps too small to be detected by the methods available, ought to be a matter of regular occurrence. In the opposite case it is conceivable that the transformation of proteins came about discontinuously, contingent upon the occurrence of numerous changes or modifications of a special kind in the germinal constitution, perhaps in connection with hapten variations. It is too hazardous, attractive as it should be, to speculate further along these lines. Yet to perceive the problem may not be superfluous and may lead to experimental investigation.

33 Landsteiner J Immunol 15 589, 1928

So far the chief reinvestigation of Nuttall's pioneering contribution has been of the relationship of the primates, because of the burning interest in this subject. A considerable part of Nuttall's work was with primate blood³⁴. Testing antihuman serums (which were so strong that they were not very specific, giving slight reactions in 14 of 97 carnivora and 11 of 40 ungulata), he obtained results in testing with the blood of 97 different primates as shown in table 2.

From this it is seen that the blood of the chimpanzee and that of the orang-utan reacts fully as well with antihuman serum as does human blood itself, in contrast with the bloods of lower primates,³⁵ which gave much less marked reactions. With a weaker and therefore more specific antihuman serum, no reactions were obtained with the blood of the lower monkeys. An antichimpanzee serum gave strong reactions with the blood of man, chimpanzee and orang-utan, but not with that of the lower primates.

TABLE 2—Results of Testing Blood of Primates with Antihuman Serums

Samples	Species	Degree of Reaction		
		Slight	Medium	Strong
34	Human (4 races)	3	7	24
8	Higher apes—Simiidae (3 species)	0	0	8
36	Old World monkeys—Cercopithecidae (26 species)	26	3	4
13	New World monkeys—Cebidae (9 species)	5	3	0
4	Marmosets—Hapalidae (3 species)	1	0	0
2	Lemurs—Lemuridae (2 species)	0	0	0

34 A few previous observations on crossed immunologic reactions between human blood and blood of lower primates had been reported by Wassermann, Grunbaum, Biondi and Ewing. Grunbaum alone compared human, chimpanzee, orang-utan and gorilla and reported that it seemed impossible to differentiate between the bloods from these four species. Friedenthal in 1905 also found it impossible to distinguish between the same four species by the precipitin reaction. In 1907, Bruck reported that according to complement fixation tests antiserum for orang-utan blood showed about the same relation to human blood as to *Macacus* blood, but was closer to gibbon (*Hylobates*) blood. Furthermore, he reported finding quantitative differences between the bloods of Europeans, Malays, Arabians and Chinese (Berl klin Wchnschr 44 793, 1907, Arb a d k Gsndhtsamte 37 618, 1907).

35 The quantitative comparisons made with the bloods of primates and their antisera by Nuttall and Strangeways are not of value because of unsatisfactory methods. Hektoen (The Precipitin Test for Blood, J A M A 70 1273 [May 4] 1918) reported a series of precipitin tests with an antihuman serum which gave a reaction with human blood in a dilution of 1:5,000, and with the blood of *Macacus rhesus* in a dilution of 1:100, whereas a large series of other mammalian bloods reacted only at 1:10. Also, he found that Rhesus hemoglobin alone of numerous mammalian hemoglobins examined (not including hemoglobins of primates higher than Rhesus) gave strong precipitin reactions with antiserum for human hemoglobin (Hektoen and Schulhof J Infect Dis 31 32, 1922 33 224, 1923).

In conclusion, Nuttall said "if we accept the degree of blood reactions as an index of the degree of blood relationship within the anthropoidae, then we find that the old world apes are more closely allied to man than are the new world apes, and this is exactly in accordance with the opinion expressed by Darwin "

This is also in agreement with Reicheit's observations on the hemoglobins, concerning which, with his permission, I quote from a letter recently received from him:

You will note in the Hemoglobin Memoir that very little attention was given to the hemoglobins of the human being and other members of the Primates. This scanty reference was due to the fact that I was preparing an elaborate memoir on the hemoglobins of the Primates, in which I had planned to go very fully into the study of the human hemoglobins, making especially exhaustive studies of the 2 different forms of hemoglobin normally present in the human blood. Such duality was found in certain other bloods, very striking and beautifully exhibited in the blood of the horse. I had done sufficient work to convince me that the hemoglobins of each genus examined were readily distinguishable from those of other genera, and that there were very positive lines of demarcation between the hemoglobins of lemurs, monkeys, baboons, apes, etc., and, moreover, that the hemoglobins of the anthropoid apes were strikingly closer to those of man than in the case of the hemoglobins of the other groups. I never published any results because I was unable for various reasons to bring my investigations to a satisfactory stage of completion.

The chief recent work in this field is reported in three papers by Landsteiner and Miller.³⁶ Having observed that antierythrocyte reactions with immune sera serve to differentiate readily between species so closely related that their blood sera are not distinguishable by the precipitin reaction, they investigated the bloods of primates by means of immune antisera, which agglutinate erythrocytes. By this means it was possible to show that while there is a close relation between the bloods of man, chimpanzee and orang-utan (gorilla blood was not tested), nevertheless by proper technic (saturation method) it was possible to distinguish between them, although this method did not serve to distinguish between the blood of white persons and that of negroes. These experiments also indicated that the difference between the blood of man and that of the chimpanzee or the orang-utan is less than between either of them and the lower monkeys. Furthermore, the blood of the anthropoids is not much if any more similar to that of the lower monkeys than is the blood of man to that of the lower monkeys. They stated that "this conclusion is in agreement with the accepted view of zoologists that man has not evolved directly from any of the existing primates, as was formerly supposed, but that the Catarrhina (Old World mon-

³⁶ Landsteiner, K., and Miller, C. P., Jr. Serological Studies on the Blood of the Primates, J. Exper. Med. 42: 841, 853 and 863, 1925.

keys), anthropoids and man have all sprung from a common stock." They supported the view that the present anthropoid apes, closely related to man as they are, do not represent direct intermediates between monkeys and man.

How much alike the bloods of man and ape really are, is strikingly shown by the observation that there is as much or more difference between the blood of horse and that of donkey in respect to immunologic behavior, as between the blood of man and that of chimpanzee and horse and donkey are so closely related that they can breed with one another, even though the product of their mating is but the lowly, infertile mule, "without pride of ancestry or hope of posterity."

Landsteiner and Miller also studied anthropoid blood in respect to the occurrence of blood groups, which have been shown to vary among the different human races, as indicated by their agglutinating effects on one another. It was found that the bloods of anthropoid apes contain groups identical with those of human blood. Of seventeen chimpanzees, three had blood of group 1, fourteen, of group 2, three, of group 3, and one, of group 4. On the other hand, the occurrence of red cell agglutinogens of the human type seems to be limited to man and the anthropoids, being differentiated from the agglutinating factors present in the blood cells of lower monkeys and other mammals. Landsteiner and Miller discussed the significance of their observations as follows:

The presence of the blood group factors in the apes has evidently a bearing on the question of the significance and origin of the blood groups in man. The literature on the subject contains two chief hypotheses, one that the blood groups were present in the different races of primitive man, the other that they arose as relatively recent mutations. If our findings in the anthropoids are taken into consideration, the simplest assumption seems to be that the isoagglutinable factors existed before man and the anthropoids were differentiated from their common ancestor. If this assumption is not made, one is forced to the conclusion that identical mutations occurred in the evolutionary lines which developed into the gibbon, orang, chimpanzee, and man at some later time.

Paleontological studies have led to the generally accepted conclusion that the existing species of man is only one of a number of human species, the rest of which have become extinct, as for instance the Neanderthal man. If the group factors had evolved before the human stage had been reached they must have been present in these various fossil human species. Either the groups were distributed among them in a manner comparable with the distribution in man of the present day or else in such wise that each species contained only a part of them.

In contemplating the latter case the question presents itself whether or not the crossing of human types more or less pure as regards the groups may have resulted in the puzzling existence in man of a few sharply defined serological qualities and in their distribution. In this respect the findings in anthropoid apes are of interest. In chimpanzees only the isoagglutinin A (of Group II cells) was encountered. Although the number of individuals examined is not large, and more extensive studies are needed, it is probable that the factor A is either characteristic for these animals or is predominant, and is present in a higher proportion

than in any known race of man. A parallel case, which can be cited, is that of the North American Indians whose bloods are almost entirely of Groups I and II.

According to Semzerva and Terechowa,³⁷ the human fetus does not possess these specific group antigens until after the sixth month of gestation, an observation which fits well with the evidence of "comparative immunology" that these characteristic human and anthropoid antigens are absent from the lower monkeys—another illustration of the recapitulation of phylogeny by ontogeny. That the biochemical structure that makes up the immunologic pattern develops during structural development is also indicated by the observation of Kritchewsky³⁸ that heterogeneous antigen for sheep erythrocytes (Forssman antigen), which is abundant in the blood and tissues of adult fowls, does not appear in the developing egg until after the fourth day of incubation.

It is unfortunate that one cannot study the immunologic relationships of fossil forms that are supposed to be ancestors of existing creatures. The only instance in which this has been possible has been reported by Friedenthal,³⁹ who found that the blood of a Siberian mammoth which had been preserved in the natural cold storage plant of arctic ice for perhaps 25,000 years gave immunologic reactions establishing its close relationship with modern elephants. Immunologic tests with extracts of the dried blood and tissues of Egyptian mummies have shown that such extracts give immunologic reactions with anti-serum for modern human blood and sensitize animals to human proteins.⁴⁰ This indicates merely that the properties that determine specificity can resist desiccation for from 2,000 to 5,000 years, and that no marked change in human proteins has taken place in that relatively short period of time.

It would be extremely interesting, if it could possibly be done, to study the immunologic reactions of extracts from insects found in amber, for Wheeler has found that ants preserved in amber believed to be millions of years old belong to genera of ants existing at the present time. So much did those ancient ants resemble the moderns that with them in the amber have been found the plant lice that they tended just as certain ants do now, and even similar parasites. Such persistence of forms without change supports Moodie's⁴¹ conclusion that a disease found in the jawbone of a fossil rhinoceros was essentially the same as the actinomycotic lumpy jaw of present-day cattle.

37 Semzerva and Terechowa. *Klin Wchnschr* 8 206, 1929.

38 Kritchewsky. *J Infect Dis* 32 192, 1923.

39 Friedenthal. *Deutsche med Wchnschr* 30 901, 1904.

40 Uhlenhuth. *Ztschr f Immunitatsforsch u exper Therap* 4 761, 1910.

41 Moodie, R. L. *Paleopathology*, Urbana, Ill., University of Illinois Press, 1923, p. 250.

It is probable that other and better opportunities may be found for studying evolutionary problems by immunologic methods if they are sought for. For example, immunologic study of forms of life that have persisted practically unchanged for vast periods, such as the horseshoe crab, the pearly nautilus and some of the mollusks, and of the related forms that have apparently been derived from these "living fossils" or their relatives, might give extremely interesting information.

EVIDENCE FROM IMMUNOLOGIC RELATIONSHIPS OF VEGETABLE PROTEINS

The vegetable kingdom may well offer possibilities that have so far been untouched. General observations on the immunologic behavior of plant proteins and crude extracts of plant tissues have shown that they behave like animal materials in respect to specificity, i. e., the strongest reactions are obtained with the same materials as are used in immunizing or sensitizing, weaker reactions are obtained with materials from closely related species and no reactions with materials from dissimilar species. This depends on the frequent presence of chemically similar antigens in closely related species,⁴² and their infrequency in unrelated species. The most extensive study by immunologic methods of the relationship of plants has been made by Mez and Ziegenspeck,⁴³ who have worked out in this way a scheme of botanical classification, which, as with animal material, shows that morphologic and biochemical (immunologic) classifications agree closely and therefore, presumably, rest on a common basis. This basis presumably is that variations in anatomic structure are associated with or dependent on differences in chemical composition.

Lewis and I⁴⁴ have had the opportunity to cooperate with Professor Gortner of the University of Minnesota in a study of the immunologic relations of certain alcohol-soluble proteins from cereal grains, with results that suggest further possibilities in respect to the use of immunologic methods in the study of evolutionary history.

Proteins soluble in relatively strong alcohol (from 70 to 80 per cent), called prolamines because rich in prolines, are not common, being found chiefly in the cereal grains, gliadin of wheat and zein of corn being perhaps the best known. A number of others have been isolated and studied by Gortner and Hoffman. They were obtained from wheat, durum emmer, einkorn, oats, barley, spelt, corn, kafir, teosinte and sorghum seeds. The chemical properties, as known from such data as

42 Wells and Osborne. *J. Immunol.* **19** 183, 1916.

43 Mez and Ziegenspeck. *Botan. Arch.* **13** 483, 1926, resumé by Mez, Leopoldina **2** 132, 1926.

44 Lewis, Julian and Wells, H. Gideon. *J. Biol. Chem.* **66** 37, 1925.

are contained in the literature and those obtained by Gortner and Hoffman, indicate that these proteins may be divided into a "wheat group," which includes the proteins isolated from the genus *Triticum*, and a "corn group," including those isolated from maize, teosinte, kafir and sorghum

The genetic behavior and nuclear structure of these cereals have been extensively studied by plant breeders, especially with the wheat group, and these studies seem to reveal interesting evolutionary relationships. It has been shown that einkorn, apparently the ancestor of modern wheat, is characterized by having seven chromosomes, that emmer and durum, presumably intermediate stages, have fourteen chromosomes, and that wheat and spelt have twenty-one chromosomes, as if their evolution had been accomplished by polymerization⁴⁵. The fertility or total or partial sterility of interspecies is said to be in accordance with these chromosome numbers. In the "corn group," it has been found that teosinte will hybridize with ordinary corn, indicating a genetic relationship.

Our immunologic results agree perfectly with the conclusions drawn from the chemical data of Gortner and Hoffman, who found that the chemical properties of these alcohol-soluble proteins indicate the existence of a "wheat group" and a "corn group of prolamines, the members of each group being chemically similar to each other. Our results also showed that these alcohol-soluble proteins from cereal grains fall into these two classes. Gliadin from wheat and rye and the prolamines from durum, einkorn, emmer and spelt, of the genus *Triticum*, seem to be closely related, apparently identical, according to all our tests. The alcohol-soluble proteins from common maize, from kafir corn and from teosinte were found to be closely related to one another, but not to the alcohol-soluble proteins of the group *Triticum*.

Accepting the morphologic evidence that modern wheat with its twenty-one chromosomes has developed from the simple einkorn with seven chromosomes, perhaps through a stage in which there were fourteen chromosomes, as illustrated by durum and emmer, one finds that through these evolutionary stages one of the most abundant and characteristic proteins of the seeds has retained a constant chemical composition.

EFFECTS OF CHEMICALS IN ALTERING DEVELOPMENT

The knowledge of immunologic processes, as well as the application of immunologic methods, also have made some, and probably will in

⁴⁵ Such mutation by polymerization has been observed in other species of plants. Thus de Vries observed that a primrose with fourteen chromosomes produced two robust mutants with twenty-one and twenty-eight chromosomes, respectively.

the future make more, contributions to the study of the processes of evolution. One thing they have done is to provide strong evidence that the strict Weismannian conception of the eternal continuity, sanctity and inviolability of the germ plasma is untenable, and that more is to be said for at least a modified form of Lamarck's doctrine of inheritance of acquired characters than a previous generation of biologists was willing to admit. Adam,⁴⁶ in his wartime Croonian lectures, delivered in 1917, brought forward various illustrations familiar to medical men of the transformation of an acquired cellular character into a permanent one transmissible to subsequent generations of cells. One of these is the striking and familiar example of the behavior of cells transformed in character, i. e., metaplasia. As every sophomore medical student is supposed to know, under the influence of chronic repeated injury, secreting columnar epithelium may resign its secretory character to take up a protective structure and function in the form of stratified, hornified epithelium. If the continued injury leads to the development of a cancer in this tissue, this cancer consists of stratified epithelium with abundant keratin, exactly like a cancer derived from the stratified epithelium of the skin or mouth. Here a recently acquired change of character and chemical composition of adult cells is perpetuated in their offspring which, before the death of their victim produce innumerable generations of descendants all carrying this artificially impressed character.

Adam also pointed out the persistence of transmission of acquired characters in bacteria. For example it takes days and sometimes weeks before bacteria take on the active dissociation of a foreign sugar, glucoside, alcohol or fat but once this power is acquired it is apt equally to be retained for generations in the absence of that particular fermentescible substance.

The immunity to infectious diseases seems to represent a similar ability of cells to transmit an acquired character to an indefinite number of subsequent generations of somatic cells. For example, a child acquires immunity to smallpox, measles or whooping cough and seventy years later the tissues of that individual the descendants of the cells that acquired whatever property it is that confers this resistance, still exhibit the same immunologic capacity. Here is an acquired property that is transmitted indefinitely in the multiplying somatic cells.

Now if the tissue cells can have reproducible qualities impressed on them by environmental conditions how can the germ cells in the same body, nourished by the same blood carrying the same influences, escape being influenced? The germ cells have to be formed from the materials

⁴⁶ Adam, J. G. Medical Contributions to the Study of Evolution. London, Duckworth & Company, 1918.

brought by the blood, and at least in the case of the male germ cells new formation is going on throughout life. It has been estimated that in the course of a reasonably active sexual life a man produces about from 300 to 500 billion spermatozoa, each one of which carries just as much power to determine the characteristics of the offspring as any one of the 400 or so ova that mature in the life time of a woman. And there is plenty of evidence that the spermatozoa, as well as the ova, may be so altered that acquired properties become inheritable. For example, there are the classic experiments of Stockard⁴⁷ showing that the scanty, runty offspring of alcoholized guinea-pigs when bred together produce in subsequent generations offspring with defective eyes, an observation in keeping with the generally recognized tendency for the existence of defects in the descendants of alcoholic human progenitors. And corroborating these are the observations of Arlitt⁴⁸ that the descendants of heavily alcoholized rats produce offspring of low mentality. Undoubtedly, these results depend on the fact that alcohol is a poison which, like lead, attacks strongly the testicles, for notoriously the testicles of human alcoholics show profound atrophy and loss of spermatogenesis, and in Arlitt's rats the testicles showed atrophy in direct proportion to the degree to which the rats had taken alcohol.⁴⁹ Furthermore, there is the evidence that injury to the germ cells by x-rays and radium leads to transmissible defects in the progeny, Bagg and Little⁵⁰ having bred mice thus affected with defects of the eyes and the feet through ten generations and obtained families with as high as 100 per cent defectives. The abnormalities were truly inherited, behaving as mendelian recessive characters.

In fruit flies (*Drosophila*), studies of the effects of x-rays have been particularly instructive, because in these creatures it is possible to observe the changes produced in the chromosomes which lead to the production of abnormal progeny.⁵¹ Mavor's⁵² experiments show that of all parts of the cell the hereditary material responds most easily to the effects of x-ray treatment, for exceptional flies that develop from eggs treated with x-rays are normal except in respect to their hereditary behavior. They prove that an external agent can "modify the mechanism of inheritance in such a way that a permanent effect is produced which

47 Stockard. *Am Naturalist* **47** 641, 1913, **50** 65 and 144, 1916, *J Exper Zool* **26** 119, 1918, *Tr Am Philosoph Soc* **62** 311, 1923.

48 Arlitt, Ada H. *The Effect of Alcohol on the Intelligent Behavior of the White Rat and Its Progeny*, *Psychol Monog* 1919, vol 26, no 4,

49 Arlitt and Wells. *J Exper Med* **26** 769, 1919.

50 Bagg and Little. *Am J Roentgenol* **10** 975, 1923, *Am J Anat* **33** 119, 1924.

51 Muller. *Science* **66** 84, 1927.

52 Mavor. *Am J Roentgenol* **10** 968, 1923.

is transmitted through successive generations" and which depends on the production in the treated eggs of an irregular distribution of the chromosomes because of changes either in the chromosomes themselves or the protoplasm surrounding them. These changes in hereditary qualities may occur without alterations in the vitality of the cells and their progeny. The fact that it has already been found that x-rays can produce mutation of genes and reorganization of chromosomes not only in fruit flies, but also in wasps, barley and tobacco raises the question whether all the mutations that have led to the vast variety of living things may not have been due to rays of short wave length and high speed particles of corresponding energy content. Muller⁵³ suggested "if so, biological evolution has been made possible only by the stray radiation present in nature—the beta and the gamma rays and the cosmic rays." The developments so far made in this intriguing field open up vast possibilities to the imagination.

IMMUNOLOGIC MODIFICATION OF DEVELOPMENT

Highly suggestive studies have been made on the possibility of another method for modifying hereditarily transmitted acquired characters, by Guyer and Smith,⁵⁴ who have used the technic of immunology in their investigations. They prepared antibodies for rabbit crystalline lens substance by immunizing fowls with pulped rabbit lenses. The antiserum was injected into rabbits at an early stage of gestation, at a time when the antibodies might possibly influence the developing lens elements of the fetal eyes. Although the mothers that received the injections suffered from no visible effects on their ocular tissues, it was found that occasionally some of their offspring had defective eyes. What is of more significance, if these offspring were bred with one another, larger and larger proportions of rabbits with defective eyes were produced in subsequent litters. The lesions consisted of opacities of the lenses, coloboma, microphthalmia, detachment of the retina, abnormal intra-ocular pressure and various abnormalities in the shape of the lenses and of the eyeballs.

Genetically, the defects of the eye behaved after the manner of a mendelian recessive character, although no pure defective-eyed strains that did not produce some apparently normal offspring had been produced in the first nine generations. However with the later generations of inbred defectives, higher and higher proportions of offspring with abnormal eyes were being obtained. Controls with animals receiving other sorts of antibodies indicate that this phenomenon truly depends on the injury to elements of the developing lens by specific antibodies for lens substance.

53 Muller. *Proc Nat Acad Sc* **14** 714, 1928

54 Guyer and Smith. *J Exper Zool* **31** 171 1920, **38** 449, 1924

Of particular significance for the whole vital problem of how inheritable variations arise from which, by natural selection or otherwise, new forms of life appear on the earth are later observations by Guyer and Smith. They took advantage of the fact, repeatedly demonstrated by immunologists,⁵⁵ that the antigenic proteins of the lens are in large part the same in different species, and not so specific for each species as are the blood proteins, so that animals can develop antibodies even for their own lenses. Rabbit lens substance was set free in the bodies of rabbits, and it was found that antibodies were produced, giving precipitin reactions with the lens substance from rabbit eyes. When such immunized rabbits reproduced, inheritable eye defects sometimes appeared in the offspring. Even needling the lens of the eye of a female rabbit may cause specific antibodies to appear in its own blood, and such rabbits sometimes produce young with defects of the eyes. Apparently to some extent, at least in rabbits the placenta is permeable to specific antibodies which can attack not only the corresponding specific structures in the fetus, but also those elements of its germ plasma that are responsible for the formation of the same structures, for how otherwise could this new property be transmissible through succeeding generations like any inheritable recessive character? That it does not depend on injury to the original maternal germ plasma is shown by the fact that a rabbit which has had an injection with antiserum for lens and has born a litter with defective eyes will subsequently bear only normal offspring. That the change in the subsequent generation is due to permanent alterations in the germ plasma is proved by the fact that it can be transmitted by males, as well as by females.

Guyer cited one case in which a male and a female, *in utero* at the time the antilens serum was injected and born with apparently normal eyes, when bred together produced offspring with defective eyes, suggesting that their germ cells had been affected by the antibodies independent of any evident damage to their own eyes.

Although awaiting confirmation and amplification by other investigators, these observations are highly suggestive as to possible ways in which variations of previously existing forms of life may have been brought about. For example, may not the production of defects of the eyes in offspring of rabbits with degenerated crystalline lens point the way to the explanation of the old problem of why fish living in dark caves are blind, a fact which has often been referred to as an apparent illustration of the production of an hereditary character from an acquired character⁵⁶. In these fish, the lens and other structures

⁵⁵ Hektoen, L. The Specific Precipitin Reaction of the Lens, J. A. M. A. **77** 32 (July 2) 1921, J. Infect. Dis. **31** 72, 1922, **34** 433, 1924.

⁵⁶ Eigenmann. The History of the Eye of the Blind Fish Amblyopsis from Its Appearance to Its Disintegration in Old Age, Mark Anniversary Volume, New York, Henry Holt & Company, 1903.

of the eye are commonly more developed in the embryos and young individuals and degenerate with age, possibly leading to the formation of antibodies with injury to the germ plasm, as in Guyer's rabbits with disorganized lenses. May not injury to other tissues than lenses also lead to the formation of antibodies capable of producing alterations in the germ plasma?

Such observations and considerations support strongly the views expressed by Adam and others⁵⁷ that the germ cells can be affected by environment, especially by chemical agents, such as toxins, antibodies, hormones, alcohol, lead and such physical agents as the emanations of radium and roentgen rays, and that in some cases, at least, the alterations thus produced when not incompatible with reproduction may persist as fixed properties in the genes. Since apparently most of the effects thus produced are detrimental and reduce the chance of survival, they tend ordinarily to self-elimination rather than perpetuation, but many congenital deformities and abnormalities seen in man may well have had such an origin, just as clinical observation has repeatedly suggested that parental alcoholism may lead to physical and mental abnormalities in the progeny.

On the other hand, certain beneficial modifications might be produced in the same way, which would tend to be preserved through natural selection. Possibly it is in some such way that species acquire a heightened capacity to resist disease, for it has been abundantly and tragically demonstrated that races or groups exposed for the first time to an infectious disease show much less capacity to resist this disease than populations long exposed to this infection. Preliminary experiments by Guyer and Smith⁵⁸ indicate that the offspring of animals immunized to typhoid bacilli for three or four generations had greater capacity to produce antibodies for typhoid bacilli than did the animals of the first generation.

When one considers the excellent work that has been done, especially in Morgan's laboratory, in tracing the changes in the chromosomes that are responsible for the production of new, inheritable characters, one must also appreciate that after all, the chromatin is a chemical compound, and whatever it does it accomplishes by virtue of the chemical properties of the chromosomes. Therefore there always is the possibility that new light may be thrown on heredity and evolution by chemical studies, whether by use of immunologic physiochemical, analytic or synthetic methods. Schmalzfuss⁵⁹ has presented an interesting dis-

57 Cunningham, J. T. *Hormones and Heredity*, New York, The Macmillan Company, 1921.

58 Guyer and Smith. *J. Infect. Dis.* **33** 498, 1923.

59 Schmalzfuss. *Naturwissenschaften* **16** 209, 1928.

cussion of the theoretical possibility of considering heredity from a chemical standpoint. It has been suggested that the agents responsible for heredity may be autocatalysts, which hasten or delay the reactions in which they participate. The chromomeres behave much like catalyzers in high local concentration through adsorption on a colloid matrix. Whatever they are, they seem to possess a remarkable constancy of behavior, and therefore of composition. Nevertheless like all the elements of the living cells they are subjected to the influences of their environment, which, as has been shown, evidently do at times modify them. If the alterations are of reversible character, as chemical changes commonly are, then the original condition may be restored as a mutation of the new forms. As chemical examples of such an alteration, Schmalfuss mentioned polymerization and depolymerization. I have already pointed out the apparent polymerization of the chromosomes in the wheat family and the primroses, and E. Bauh has assumed the same thing in the color modifications of snapdragon (*Antirrhinum L.*). Another chemical analogy is furnished by the mutual buffering and debuffering of salt mixtures. Of course, physical alterations may also be reversible as in the change from gel to sol and the reverse. As Schmalfuss pointed out, the recognized linear arrangement of the hereditary substance in the chromosomes is not incompatible with the occurrence of physical alterations without change in the order of the different factors, just as in a string of pearls individual pearls may be rotated or the entire string altered in shape by bending without altering the linear arrangement. He also pointed out how in experimental production of melanin by the action of enzymes, oxygen and water on dioxyphenylalanine the various types of melanin formation or its absence (albinism) that are familiar in studies of genetics can be simulated on a purely chemical model, with hybrids, dominants and recessives. He predicted that in the near future a systematic consideration of "developmental chemistry" will arise, throwing light on the problems of heredity and evolution.

Even now one sees from these first feeble steps in the lives of new sciences that their application to the problem of the origin of life and its evolution warrants hope that from this unexpected direction may come also weighty contributions to knowledge as to how some pathologic states may arise, and also how living forms have been able to evolve mechanisms protecting them from their environment and their diseases. The student of biologic evolution may give fully as much to medical science as biochemistry and immunology promise to give to him when he has learned to use these tools. Any progress in any one division of the biologic sciences carries along with it all the other divisions, and most surely the all-including division of medicine.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths—Clarence C Little has been elected president, Francis Carter Wood vice-president, and William H Woglom secretary-treasurer of the American Association for Cancer Research

Henry Albert, professor of pathology and bacteriology in the University of Iowa from 1903 to 1922, and commissioner of health for Iowa since 1926, died April 6, 1930, following an operation for appendicitis, at the age of 52 years

Raymond C Parker, formerly associated with cancer research at the University of Pennsylvania, has joined the scientific staff of the Rockefeller Institute for Medical Research

C C Twort has been appointed director of cancer research at the University of Manchester

Katsusaburo Yamagiwa, professor of pathology in Tokyo Imperial University, who produced tar cancer in rabbits—a wonderful achievement—died March 2, 1930 It is hoped to give more details about Professor Yamagiwa in a subsequent issue

The following appointments are announced by the department of ophthalmology, Washington University, St Louis, in connection with research on trachoma and other ocular infections George H Bishop, professor of applied physiology, Louis A Julianelle, associate professor of applied bacteriology and immunology, James A Hawkins, associate professor of applied biochemistry, R W Harrison, instructor in applied bacteriology and immunology, G Bowers, assistant in applied bacteriology

The Cameron Prize of the faculty of medicine of the University of Edinburgh for 1930 has been awarded George R Minot and William P Murphy, Boston, for their work on the treatment for pernicious anemia with liver

Further Provisions for Research on Cancer—On March 17, 1930, a new institute for cancer research was opened at Villejuif, near Paris A new hospital is in course of construction beside the institute

The legislature of Saskatchewan has established a permanent cancer commission to secure better education of the public in regard to cancer, and better facilities for the diagnosis and successful treatment of cancer

Symposium on the Kidney—A symposium on the kidney in health and disease is to be held in Minneapolis, July 7 to 18, 1930, under the auspices of the medical school of the University of Minnesota The object is to secure better correlation of views and cooperation between the many highly specialized workers on problems connected with renal physiology and pathology

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EFFECT OF SUCCESSIVE RADIATIONS WITH THE MERCURY ARC ON THE WHITE BLOOD COUNT OF NORMAL RABBITS MARY HARDY and JEANNETTE CHAPMAN, *Am J Hyg* **10** 655, 1929

It was found that although single massive doses of ultraviolet radiation produced characteristic changes in the blood count, a dose of 12 lithopone units given daily for eight days produced no appreciable change in the total leukocyte or lymphocyte and polymorphonuclear counts

JOHN PHAIR

THE RELATIONSHIP OF THE CERVICAL SYMPATHETIC NERVES TO THE CEREBRAL BLOOD SUPPLY STANLEY COBB, *Am J M Sc* **178** 528, 1929

All the evidence taken into consideration, it would seem that vasomotor control of at least the superficial cerebral vessels is now established. One must be guarded, however, in drawing clinical conclusions. Physiologically, it has been shown that pial vessels may constrict or dilate in response to appropriate stimulation, but in anesthetized animals the changes are not of great magnitude, and may be overcome by large variations in systemic pressures. L. Hill's statement, strictly speaking, still holds: "There is no evidence of a causation of cerebral anemia by spasm of the cerebral arteries." Real, obliterating angiospasm has only been experimentally observed when vessels are strongly and locally stimulated under nonphysiologic conditions (Florey, 1925; Wolff, 1927; Lenox and Cobb, 1928). Recent investigations, however, certainly make vascular spasm a much more reasonable working hypothesis than it was thirty years ago.

AUTHOR'S SUMMARY

RELATION OF THE ADRENAL GLAND TO THE TOXEMIA OF INTESTINAL OBSTRUCTION R. A. CUTTING, *Arch Surg* **19** 272, 1929

Bilateral adrenalectomy was performed on a series of rabbits, and material from obstructed loops of the intestine of other rabbits was injected into these and their controls. It was found that the adrenalectomized rabbits, although they did not exhibit as severe symptoms as their controls, nevertheless succumbed much more rapidly to toxemia. From his experiments, the author feels that the adrenal glands subserve a definite function in combating the toxemia of intestinal obstruction. Animals with intestinal obstruction showed early degenerative changes in the adrenal glands, so that if these glands do have a detoxifying activity, the attack on intestinal obstruction should be made early to avoid damage to the adrenals.

N. ENZER

INTESTINAL OBSTRUCTION F. RAINE and M. C. PERRY, *Arch Surg* **19** 478, 1929

The authors worked on rabbits. They found that rabbits die of intestinal obstruction much more rapidly than dogs, largely because the former do not vomit. The release of the obstruction, when it had been made temporary, usually permitted the animal to return to health, and the reabsorption of the contents of the obstructed loop through normal intestine apparently initiated a rapid return to normal. This may be due to the reabsorption of the chlorides. When the pressure in the obstructed loop was reduced, the duration of survival was increased. They feel that release of pressure increases reabsorption and diminishes secretion. The therapeutic value of administering sodium chloride increases with the release of pressure and diminishes as the interintestinal pressure increases.

N. ENZER

CORRELATIONS OF INTERNAL AND EXTERNAL PANCREATIC SECRETION G DE
TAKATS and I T NATHANSON, Arch Surg **19** 771, 1929

The article is subdivided into three sections, the first giving a review of the literature and an outline of the problem, and the second a description of the histologic changes which occur when the tail of the pancreas is isolated from the body by division either through ligature or more especially after the use of the cautery.

The observations may be briefly summarized as a progressive fibrosis and connective tissue replacement of the acini and ducts, with an apparent increase in the number of islands. The mechanism has its onset with an early edema and distention of the parenchyma, followed by a slowly progressive necrobiosis. The acini disappear first, and, while they do not entirely disappear, the ducts become small and widely separated. The connective tissue proliferation begins first between the lobules, and then becomes more diffuse and invading until finally the tail is represented by a dense, sclerotic cord. The islands are also involved in the edema, but as the sclerotic process progresses, new islet-like formations appear, and while not absolutely characteristic, these possess the staining properties and vascular arrangement of the island. In this experiment a portion of the tail, after separation, was transplanted into the omentum, and was found to survive for at least three months.

In the third division the effect on the blood diastase of ligating the tail was studied and it was found that after ligation there was a short preliminary rise, followed in a few days by a larger, secondary rise in the diastase of the blood. The increase varies with the amount of the pancreas isolated, and if both the head and the tail are ligated, the rise is sudden and maximum and is not followed by a secondary increase. This test appears to be a sensitive index of acute pancreatic obstruction. In the dogs studied the diastase value was returned to normal usually by the end of two weeks.

N ENZER

OXYGEN CONTENT OF BLOOD IN PATIENTS WITH VARICOSE VEINS A BLALOCK,
Arch Surg **19** 898, 1929

The carbon dioxide and oxygen content of venous blood obtained from the femoral veins of normal patients and from varicose veins were compared. In unilateral varicose veins, it was found that the blood from the diseased vein had a higher oxygen content than from the normal vein on the opposite side. This was true of the blood obtained when the patient was in the standing or recumbent position. From normal veins, the oxygen content is highest when the patient is in the recumbent position, and decreases rapidly when he assumes the upright position. When the patient changed from the recumbent to the upright position, there was a smaller drop on the diseased side than on the normal side. It seemed also that the oxygen content was higher in the blood obtained from veins draining ulcerated areas, but too few cases were studied in respect to this. Similar results were obtained in a case of thrombosis of the inferior vena cava associated with dilated veins in the lower extremities. The author points out that these observations suggest an increase in the total flow of blood through a leg with varicose veins.

N ENZER

STUDIES ON THE EFFECTS OF OVERDOSAGE OF VITAMIN D R F LIGHT, G
MILLER and C N FREY, J Biol Chem **84** 487, 1929

The administration of an excessive amount of viosterol may result in a drainage of mineral constituents from the body, with a relatively greater elimination of phosphorus than of calcium. The daily ingestion of 100,000 minimal effective doses may be followed in the rat, by anorexia, emaciation, greasy hair, labored breathing, and eventual death. No ill effects appear to attend the administration, to the rat, of 10,000 times the daily curative dose.

ARTHUR LOCKE

THE PATHOLOGICAL ACTION OF LIGHT A G LEVY, J Path & Bact **32** 387, 1929

The essential action of white light on sensitized tissues and of ultraviolet light on nonsensitized tissues appears to be identical. The result of prolonged irradiation of the mouse's ear is an immediate complete stasis, with subsequent necrosis. The result of less prolonged irradiation is a delayed stasis, with subsequent necrosis. In no case is stasis conditioned by the formation of clots. It is due to an inflammatory reaction, accompanied by extravasation of plasma from the vessels and consequent aggregation of corpuscles. The necrotic changes are a consequence of the cessation of circulation. The coagulation of extravasated plasma is a consequence of circulatory arrest. Hardening of the dead tissue is due to mechanical desiccation. Hypertrophy and infiltration of the epithelium are striking results of irradiation which is insufficient to produce general stasis. The hypertrophy is definitely shown to result from a brief period of irradiation.

AUTHOR'S SUMMARY

EXPERIMENTS TO DETOXYFY CHLOROFORM H FUHNER, Deutsche med Wchnschr **55** 1331, 1929

White mice exposed for three hours to a certain concentration of chloroform vapor containing 1 per cent alcohol died on an average in one and a half days. Mice that were treated similarly but with 10 per cent alcohol added to the chloroform died usually in from four to six days. Alcohol inhibits the oxidation of chloroform to phosgene, and this is thought to account for the lower toxicity of chloroform to which more alcohol has been added.

PAUL J BRESLICH

GOITER IN RUSSIA A GEOGRAPHICAL-PATHOLOGIC CONTRIBUTION H J ARNDT, Verhandl d deutsch path Gesellsch **24** 97 1929

One thousand one hundred and four specimens of normal thyroids and goiters were studied in different goiter-free and in most of the goiter districts of Russia. Endemic goiter was encountered not only in mountainous but also in level regions. In Moscow 18 per cent of the cases had adenomas, in Perm one fourth, in Tiflis two fifths and in Irkutsk about one half of the cases. The goiter-free thyroid gland in Russia does not show the small follicular structure, so typical for the thyroid gland in Switzerland. Only in White Russia and East Siberia, marked epithelial proliferation is noticed in the normal gland.

Most of the patients with goiter who were operated on in Moscow presented severe or mild thyrotoxic symptoms. The goiters obtained from these patients did not correspond with the classic histologic description of exophthalmic goiter, but were diffuse colloid goiters with epithelial proliferation. In Petrograd and Charkow, the conditions were much the same.

In the endemic region of White Russia, three fourths of the goiter material consisted of macrofollicular diffuse colloid goiters, in the Volga Valley, on the other hand, the nodular goiter was prevailing. In the Ural Mountains, the diffuse and nodular colloid goiter is common, without causing disturbance of the thyroid function. In the Northern Caucasus Mountains the diffuse colloid goiter with epithelial proliferation is common, and here it is often accompanied by thyrotoxic symptoms. In the territory of Tiflis (Transcaucasia) most of the goiters, obtained by operation, were adenomatous. In East Siberia, parenchymatous (fetal) adenomas prevail, clinically there are mild cases of hypothyroidism present. In Middle Asia (Teshkent) the adenomatous goiters are still more common and, in these regions, true cretinism is more frequently encountered.

The morphology and function of the type of goiter that occurs in Russia resembles that of the goiter found in Southern and Central Germany. The most characteristic form of the goiter in Russia is the macrofollicular colloid goiter.

with epithelial proliferation, with or without small colloid nodules. This form predominates in the endemic regions of the plains and in mild endemic regions of the mountains. In so-called goiter-free regions this colloid goiter is often associated with clinical symptoms of severe or mild grades of exophthalmic goiter.

In Arndt's material twenty-eight different races or nationalities are represented. He denies a true race disposition for goiter and believes that exogenic factors, especially nutrition and standard of living, play a much more important rôle in the etiology of goiter.

C. A. HELLWIG

ARTIFICIAL PRODUCTION OF CORPUS LUTEUM BY INJECTION OF PLACENTAL SUBSTANCE. M. MURATA and K. ADACHI, *Ztschr. f. Geburtsh. u. Gynak.* **92** 45, 1927

The injection of an emulsion or extract of placenta from an early period of pregnancy of hydatiform mole and of malignant chorio-epithelioma produces corpora lutea in rabbits. There are two types of corpora lutea, those originating from ruptured follicles and those from nonruptured ones. The efficacious substance is derived from the chorionic epithelium. This incretion apparently prevents the regression of the corpus luteum during pregnancy. The corpus luteum producing quality of the incretion, as observed in the test animal, is an expression of the same effect as is shown in its specific stimulating influence on the granulosa cells. These are transformed into lutein cells simultaneously with a change of the follicle into a corpus luteum. The transformation of a follicle into a corpus luteum and the ovulation are, therefore, two processes independent of each other. The polycystic degeneration of the ovaries as observed in hydatiform mole and chorio-epithelioma can be compared with the artificial production of corpora lutea.

W. C. HUEPER

THE EFFECT OF THE SERUM OF PREGNANT WOMEN ON THE MALE SEXUAL ORGANS. E. FELS, *Ztschr. f. Geburtsh. u. Gynak.* **93** 50, 1928

The serum of pregnant women was injected into male mice. The female sexual hormone impairs the growth of the heterologous sexual glands. This antagonistic effect is apparent only in organs still in the developmental stage. It is not effective in adult organs. The serum activates also the development of the seminal vesicles, prostate and penis by the large amount of the anterior pituitary hormone present in the serum. This acts directly on the interstitial cells of the testicle which proliferate. Therefore as producers of the male sexual hormone the interstitial cells play an important role.

W. C. HUEPER

Pathologic Anatomy

HEMORRHAGES FROM LACERATIONS OF THE CARDIAC ORIFICE OF THE STOMACH DUE TO VOMITING. G. K. MALLORY and S. WEISS, *Am. J. M. Sc.* **178** 506, 1929

Severe, occasionally fatal, gastric hemorrhage with hematemesis may occur after periodic alcoholic debauches. Acute lacerations with ulcerations at the cardiac opening of the stomach were the sources of such fatal gastric hemorrhages in three patients here described. Lacerations of the cardiac opening of the stomach leading to massive hemorrhage may also develop in other diseases, for example, pernicious vomiting of pregnancy and malignant neoplasms, if associated with persistent nausea, retching and vomiting. The responsible etiologic factors producing the described lacerations are pressure changes in the stomach during a disturbed mechanism of vomiting, and continuous regurgitation of gastric juice over the mucosa of the cardia. The local irritant and astringent effect of alcohol as well as the nature of vascularity of the mucosa involved are also

predisposing factors In the presence of obscure gastric hemorrhage, or of hematemesis, lesions of the cardiac opening of the stomach should be thought of, and in case surgical interference is undertaken the folds of the cardia should be explored carefully

AUTHORS' SUMMARY

SPONTANEOUS INTRACRANIAL HEMORRHAGE FROM A VASCULAR TUMOR R J REITZEL and P BRINDLEY, *Am J M Sc* **178** 689, 1929

A case of fatal intracranial hemorrhage from a cerebral vascular telangiectasia in a young man is reported, with observations at autopsy, and a brief review and discussion of the literature A vascular tumor should be borne in mind as a possible source of intracranial hemorrhage when such hemorrhage occurs in a previously healthy young adult

AUTHORS' SUMMARY

CEREBRAL HEMORRHAGE FROM VENOUS AND CAPILLARY STASIS STANLEY COBB and JOHN P HUBBARD, *Am J M Sc* **178** 693, 1929

Five cases are presented which at autopsy showed hemorrhage into the parenchyma of the brain In all of these the extravasation came from the veins and capillaries, there is no evidence that blood escaped from arteries The mechanical factor common to all these cases is venous stasis, the common chemical factor is asphyxia It is pointed out that widespread lesions can be caused by these two factors, the unit lesion being a petechial extravasation, but large lesions are formed by coalescence, and frank venous hemorrhage may be found Such cases are more common than is generally supposed

AUTHORS' SUMMARY

OBLITERATIVE CHANGES OF THE PULMONARY LYMPH VESSELS IN TUBERCULOSIS J DWIGHT DAVIS, *Am Rev Tuberc* **19** 595, 1929

A thrombus occasionally forms in lymph vessels which drain the area of a tuberculous focus in the lungs It is due to sensitivity of the endothelial lining of the vessel, and results in proliferation of the endothelial cells with a formation of fibroblasts The formation of the thrombus continues until the lumen of the lymph vessel is densely packed with these fibroblastic cells Following this and without organization, degenerative or retrogressive changes occur Usually these changes appear as a vacuolization and replacement of the cell by fibro-elastic tissue, or by a transformation of the fibroblasts into hyaline material Canalization of the occluding mass also is seen This proliferation is entirely separate from the formation of tubercles within the lymph vessels, which also may occur The type of proliferation, although it is due to the stimulation of tuberculous products, is not distinctive, and in itself it would not be known to be of tuberculous origin

H J CORPER

REPORT OF FIFTY AUTOPSIES IN WHICH THE PRIMARY CAUSE OF DEATH WAS PULMONARY TUBERCULOSIS AUDLEY O SANDERS, *Am Rev Tuberc* **20** 128, 1929

A summary report of fifty autopsies is presented, only those cases being included in which gross tuberculous pulmonary lesions were extensive and in which there was no doubt that the tuberculous lesions were the primary cause of death Forty-five of the patients were white and five colored The ages ranged from 26 to 62 years The cases included one of tuberculosis of the bones and joints, two of chronic purulent otitis media and eighteen of laryngeal tuberculosis No gross abnormality of the thyroid was noted in any case In forty-one cases there were bilateral pleural adhesions, and in nineteen, pneumothorax, which in ten instances was therapeutic All but three of the fifty cases showed

gross bilateral pulmonary lesions, thirty-two having more or less extensive bilateral cavitation, sixteen unilateral cavitation and two no cavities. In general, the size of the heart and condition of the cardiac musculature corresponded closely to the degree of general nutrition and the muscle tone. In twenty-two cases there were slight atheromatous changes in the aorta, while in three there was marked atheroma. In sixteen cases the peritoneal cavity contained fluid, in nine of them there was pleural effusion, the effusion being pericardial in five. No definite tubercles or caseous nodules were found in the livers, but there were two cases of cirrhosis of the liver, in both of which there was an alcoholic history. No gross or evident pathologic change was noted in the gallbladder in any case. No pathologic change was noted in the pancreas in any case. In nine cases there were definite changes in the spleen and in one case the left suprarenal body was enlarged. In six cases tuberculous lesions were found in the kidney, in three instances they were bilateral. Extensive involvement of the bladder was observed in two cases and anomalous kidneys were found in one. Of nine cases in which extensive lesions of both the small and the large intestine, were observed, no note was made in the clinical records of any bowel symptoms except moderate constipation in three cases, abdominal distress alone in one case and abdominal distress together with diarrhea in five cases. Of ten cases with lesions only in the small bowel no abdominal symptoms were recorded clinically in four cases, moderate constipation in two and abdominal distress with diarrhea in four. Of two cases with lesions only in the cecum and the colon, no mention was made of abdominal symptoms in one and diarrhea was noted in the other. Of the fifty cases, the clinical records reported thirteen with notable diarrhea, tuberculous intestinal lesions were found in ten of these thirteen at autopsy.

H J CORPER

HISTOLOGY OF HEALED PRIMARY TUBERCULOUS LESIONS OF THE LUNG R H JAFFE and S A LEVINSON, *Am Rev Tuberc* 20 214, 1929

The tendency of the tuberculous primary lesion of the lung to become replaced by bone is explained on the basis of an irritating action of the calcified center on the specific capsule. This irritating action leads to an ingrowth of granulation tissue, which, bathed with tissue fluids saturated with calcium salts, undergoes osseous metaplasia. This metaplasia is characteristic of the primary lesion and is perhaps due to its peculiar histogenesis. It is seldom observed in the calcified and encapsulated tubercles of regional lymph nodes and of reinfections.

H J CORPER

BENIGN TUMORS OF THE FEMALE BREAST G VAN S SMITH and G A MARKS, *Surg Gynec Obst* 49 316, 1929

A clinical and pathologic study of 201 cases of benign tumors of the breast led to the following conclusions:

Periductal or intracanalicular adenofibromas were present in 28.3 per cent of cases, occurring usually in patients under 30 years of age, 7 per cent were associated with sarcoma and 13 per cent were bilateral.

Fibrocystadenomas or fibroadenomas occurred in 7.9 per cent of the patients, all of whom were under 35 years of age, 14.2 per cent had a discharge from the nipple, and 28 per cent were associated with carcinoma.

Papillary cystadenomas occurred in 6.9 per cent.

Chronic cystic mastitis occurred in 56.7 per cent of the specimens. The patients were all over 35 years of age, 8.8 per cent had a discharge from the nipple, and 3.4 per cent were bilateral.

Abnormal menstruation occurred in 42.3 per cent of those who had not passed the menopause.

RICHARD A LIFVENDAHL

THE HISTOGENESIS OF ADENOMYOSITIS G L MOENCH, Surg Gynec Obst
49 332, 1929

The author is of the opinion that many of the areas containing glands which are surrounded by an endometrial stroma-like tissue are not necessarily evidences of endometriosis. In some instances he regards them as serous peritoneal cysts surrounded by an inflammatory reaction, whereas others are normal occurring embryonal tubules. Those cysts that are located in the lower part of the vagina and the hymen he regards as being derived from the wolffian duct. The various theories which have been propounded to explain these variously located adenomyositic lesions are discussed.

RICHARD A LIFVENDAHL

DISLOCATION OF THE TESTIS E P ALAEA, Surg Gynec Obst 49 600, 1929

Traumatic dislocation of the normally situated testis is dependent on three factors: (1) anatomic factors such as, an atrophic testis, relaxation of the external inguinal ring or the presence of an inguinal hernia, (2) obstruction at the scrotal neck, inguinal or perineal regions, and (3) the direction and the force of the blow. Thus, if a subcutaneous course is taken, the organ may come to rest in the pubic, superficial inguinal, penile, crural or the perineal regions. If the path is through the inguinal canal, it may lodge here, intra-abdominally, or in the femoral canal. To these two groups, the author adds a third to which he applies the term "compound dislocation of the testis," in which the testis is forced through a tear in the scrotum. He reports one case of this type and quotes three similar instances from various authors. The writer's other patient presented a very unusual condition in that the testicle was located over the fascia in the region of the apex of the femoral triangle and 12 cm below the external inguinal ring. The twenty-three original occurrences of traumatic dislocation of the testis collected from the literature, since 1800, is reviewed in detail.

RICHARD A LIFVENDAHL

KRUKENBERG TUMOR OF THE OVARY R FALLAS, Surg Gynec Obst 49
638, 1929

The typical gross and microscopic picture of two cases of Krukenberg tumor of the ovaries is added to the literature. In one, exploration of the upper part of the abdomen revealed an indurated area in the stomach. The second is unusual in that no primary source in the gastro-intestinal tract could be determined, clinically, however, cells characteristic of these tumors were found in a rapidly growing tumor of the breast in this patient. The possibility of the ovarian growths being secondary to the neoplasm of the breast is considered. Nothing new is added to the previous theories as to the path of transmission of these tumor cells to the ovaries.

RICHARD A LIFVENDAHL

EMBRYONAL ADENOMYOSARCOMA OF THE KIDNEY IN AN ADULT E F KIL-
BANE and C W LESTER, Surg Gynec Obst 49 710, 1929

Embryonal adenomyosarcoma (Wilm's tumor, embryonal adenocarcinoma or embryonal sarcoma) of the kidney occurs usually during infancy, but the writers report this type of tumor in a man, aged 48, which makes the sixteenth case on record that has been reported in adults. Grossly, the tumor was characteristic in that it was large, being 16 cm in diameter, weighed 980 Gm, was sharply separated from the remaining renal tissue by a connective tissue capsule, and was centrally necrotic. The connective tissue elements had the appearance of a rapidly growing sarcoma, the epithelial structures were composed of malignant appearing oval cells arranged in cords and tufts or cuboidal cells assuming a tubular fashion, and the muscle fibers were in the form of slender strands. No

striated muscle, bone or cartilage were found, as has been previously recorded in these neoplasms. Following the removal of this kidney, there were local subcutaneous recurrences of the epithelial elements in a sinus through the skin at the operative site.

RICHARD A. LIFVINDAHL

ANATOMIC OBSERVATIONS IN CHOKED DISK FROM MYELOGENOUS LEUKEMIA
P. A. JAENSCH, Arch f Ophth **122** 618, 1929

Changes in the eye as a result of leukemia are well known. The anatomic observations, however, have been less frequently published. The author has seen five myelogenous leukemias and one aleukemic lymphadenosis with retinal hemorrhage.

White spots and frequently prominent hemorrhages, discoloration of the fundus to orange-red, distention of the veins and changes in color of the blood vessels have been described.

In addition to normal observations, the disk showed every transition stage from blurring of the borders and neuritis of the optic nerve to formation of a high grade choked disk. These observations are true for both myelogenous and lymphatic leukemia. The choroid, however, shows distinguishing features for the two conditions. In lymphatic leukemia there is a diffuse infiltration of the stroma, the choroid may be thickened to four or five times its normal condition. Blood vessels are usually empty and of normal caliber, sometimes their walls are infiltrated.

In myelogenous leukemia, the similarly distended choroid is due to an engorgement of the blood vessels, but in the choroid stroma, which is usually very meager, no cells can be demonstrated. The excessive number of intravascular cells may be so great that the vascular walls cannot be recognized by the usual staining method, and only a demonstration of elastic fibers shows that all the white blood cells lie within the vessels.

The author gives a full description of observations in the myelogenous leukemia (secondary myeloblastic leukemia) of a boy, aged 9 years, in whom both bulbs showed signs of a high grade choked disk. The dilated veins and capillaries of the entire uvea and of the retina and disk as well as of the optic nerve were engorged. Cells showing fatty degeneration were found in two places and were thought to be derived from the histiocytes and not connected with the basic disease.

CHARLES WEISS

GENERALIZED MILIARY LYMPHOGRANULOMATOSIS O. GSELL, Beitr z path Anat u z allg Path **81** 426, 1928

A man, aged 53, had become gradually and progressively weaker and emaciated during the year preceding his death. Two weeks before death he became jaundiced. There had been no local symptoms, and on admission to the hospital in a moribund condition no external changes except jaundice and emaciation were to be noted. Records of the blood picture and of the temperature were wanting. At necropsy the lungs were studded by innumerable small nodules, which suggested miliary tuberculosis. The liver was enlarged to 35 Kg and contained multiple larger, pale nodules, up to the size of a fist, which suggested metastatic tumors. In the moderately enlarged spleen were nodules larger than those in the lung and smaller than those in the liver, together with diffuse changes, which suggested lymphogranulomatosis. On microscopic examination, the nodules of the lung were found to be composed of lymphocytes, fibroblasts, proliferated endothelium, a few eosinophils and large cells of the Sternberg-Dorothy Reed type, all embedded in a fibrillar reticulum. Histologically, the miliary nodules were typical lesions of lymphogranulomatosis. Amyloid material was present in them in the form of streaks and masses. Microscopic lesions of the same kind were present everywhere in all the tissues except those of the myocardium, brain, suprarenal glands and prostate. The larger nodules were of the same general histologic structure as the miliary ones, except that they contained a larger amount of collagenous tissue.

At the periphery of the large nodules the tissue was identical with that of the miliary and microscopic lesions. The periportal lymph nodes were enlarged. The case is considered one of lymphogranulomatosis with unusually generalized distribution, involving the lymphoid and areolar mesenchymal tissues throughout the body. Amyloid deposition in lymphogranulomatous lesions has been previously described, but occurs infrequently.

O T SCHULTZ

PARIETAL ENDOCARDIAL SCLEROSIS A. BOGER, Beitr z path Anat u z allg Path **81**.441, 1929

On the basis of selected examples described in detail, Boger discusses the nature and origin of sclerosis or thickening of the parietal endocardium, so-called chronic parietal endocarditis. According to its gross characteristics, the condition discussed may be divided into the diffuse and the localized, and according to its etiology into the inflammatory and noninflammatory. The diffuse thickening of the parietal endocardium involves an entire chamber or more than one chamber. It is not inflammatory in nature and is the result of the reaction of the elastic and connective tissue of the endocardium to dilatation of the chamber. It is usually not associated with inflammatory changes in the valves, although such association may be noted if the valvular involvement has led to dilatation of a cardiac chamber. Increase of both elastic and collagenous tissue elements characterizes the process histologically. Localized areas of endocardial thickening are usually inflammatory in origin and are associated with inflammatory changes in the wall of the heart. Most often the localized process is the result of contact of the parietal endocardium with an inflamed valve, most commonly with the posterior surface of the aortic segment of the mitral valve. Involvement of a localized area of parietal endocardium by direct continuation of an inflammatory process from the myocardium was not observed in Boger's series of cases, but the possibility of its occurrence is granted. The purely functional, noninflammatory origin of localized endocardial thickening is denied by the author, who also denies the formation of endocardial pockets as a primary process. Such pockets are the result of the action of the blood stream on the ridges of localized areas of endocardial thickening.

O T SCHULTZ

NATURE OF TUBERCULOUS CASEATION H. SCHLEUSSING, Beitr z path Anat u z allg Path **81** 473, 1929

Coagulation necrosis was first described by Weigert in 1879 and repeated observations on it as a pathologic process are to be found in his later writings, especially those to 1891. Tuberculous caseation was considered by Weigert a form of coagulation necrosis, that is, a form of sudden tissue death characterized by coagulation of cellular protoplasm, which need not necessarily show any great pathologic alteration before it undergoes coagulation. Schleussing claims that, although later writers still include tuberculous caseation among the examples of coagulation necrosis, their morphologic descriptions are not entirely in accord with those of Weigert and emphasize the occurrence of cellular degenerative changes, such as cloudy swelling, fatty change and nuclear fragmentation as necessary antecedents to caseation. Believing that such views would make caseation a process different from the coagulation necrosis described by Weigert, he made a morphologic study of caseating tuberculous lesions and attempts an interpretation of the nature of the process. Although cellular degenerative changes are not unusual in such lesions, their chief morphologic characteristic is, as was maintained by Weigert, the retention of cell contours and of the outlines of tissue elements, especially swollen collagen fibers, in the dead tissue. The sudden tissue death is the result of the action of an excessive dose of or excessively strong toxin, or of greater susceptibility of the tissue to the action of toxic material. The essential factor in the coagulation is the presence in the tissues, both within and outside the tissue elements, of an increased amount of fluid capable of coagulation. Caseation differs from ordinary sudden necrosis, such as may sometimes

also be caused by the tubercle bacillus, in that it occurs in an inflammatory tissue Huebschmann, Medlar and others considered ferments liberated by leukocytes important in the coagulation Schleussing was not able to convince himself of the importance of this factor He considers the inflammatory edema of an allergically hypersusceptible tissue as the underlying phenomenon of tuberculous caseation, which is a typical coagulation necrosis as defined by Weigert

O T SCHULTZ

THE ALVEOLAR EPITHELIUM OF THE LUNG G SEEMANN, Beitr z path Anat u z allg Path **81** 508, 1929

One of the most actively discussed problems in contemporary scientific medical literature relates to the origin and nature of the phagocytic cells of the lung Three views are extant, that which derives these cells from the respiratory alveolar epithelium, that which derives them from the capillary endothelium and that which derives them from the septal histiocytes In the course of the controversy, there have arisen some investigators who deny entirely the existence of any epithelial lining within the alveoli of the lung This view, however, is not a new one, it is the original view of the structure of the lung, as championed by Zenker and Villemun, who considered the lung a mesenchymal structure devoid of epithelium except in the bronchi It was Kolliker, who, in the early eighties of the past century, as the result of intrabronchial silvering, described an alveolar lining composed of smaller nucleated cells separated by flattened nonnucleated plates This specific respiratory epithelium was entodermal in origin Aschoff and his school have taken a stand for the origin of the phagocytes of the lung from the alveolar epithelium, and Seeman, in a previous paper from Aschoff's laboratory, concluded, from vital staining methods, that the phagocytes of the lung are derived from alveolar epithelium but constitute a biologic cell type *suu generis* The present work is a histologic study undertaken to determine the existence of alveolar epithelium The methods used were silvering of fresh lung tissue by intrabronchial injection of silver nitrate solution, intracapillary silvering of the tissue by the injection of silver nitrate solution into the pulmonary artery, demonstration of the reticulum of the septums, and histologic study of the embryonic lung As the result of his study, Seemann claims that intrabronchial silvering stains electively, and specifically the alveolar epithelium Intracapillary silvering stains electively the capillary endothelium, and the two methods permit a sharp topographic distinction between capillary endothelium and alveolar epithelium The capillary endothelium is covered by a fenestrated membrane which has the staining properties of reticulum The epithelium does not form a complete layer When it is present, the epithelium is separated from the endothelium by the reticulum membrane The nonnucleated respiratory epithelial plates, described by Kolliker, do not exist, in areas in which epithelium is not present, the reticulum membrane is devoid of covering Seemann claims that intrabronchial silvering after irritation of the lung brings out clearly the epithelial origin of the phagocytic cells He denies that the alveolar epithelium present has any respiratory function, but ascribes to it a protective function, manifested by its great phagocytic activity In the embryologic development of the lung, the transformation of a complete lining layer of cuboidal alveolar epithelium into an incomplete lining formed of separated flattened epithelial cells can be followed

O T SCHULTZ

FATE OF INJECTED HOMOLOGOUS LEUKOCYTES E CHRISTELLER and G EISNER, Beitr z path Anat u z allg Path **81** 524, 1929

This is what was apparently to be the first report of a line of experimental investigation on which Christeller was engaged at the time of his sudden death The origin of inflammatory exudate cells, ascribed to the blood stream by Cohnheim, has aroused renewed interest because of recent work which derives such cells from local tissue elements, the adventitial cells of Marchand, the slumber

cells of Grawitz, the tissue histiocytes and the tissue lymphocytes Christeller and Eisner hoped to approach the problem of the participation of circulating leukocytes in inflammatory exudate by using homologous leukocytes which they could recognize in the vessels and tissues of a recipient animal Sterile subcutaneous abscesses were produced in dogs by the injection of 1 cc of turpentine Two days later, 10 cc of a 2 per cent solution of trypan blue was injected directly into the abscess Fifteen minutes later the pus, which consisted largely of stained leukocytes, was withdrawn, washed in sodium chlorid-sodium citrate solution, suspended in this solution and used for intra-arterial or intravenous injection into normal recipient animals The animals were killed from two to seven minutes after injection of the leukocytes, and the tissues were examined microscopically to determine the distribution of the marked leukocytes In general it was found that many of the leukocytes tended to attach themselves to the endothelium of the capillaries of the territory of the vessel selected for injection Many, however, entered the general circulation These were quantitatively removed from the blood by the capillaries of the lung in the first passage of the blood through the lungs The removal of damaged cells from the blood is considered an important function of the pulmonary capillary circulation When marked leukocytes were injected into recipient animals in which sterile abscesses were caused by turpentine, none of the stained leukocytes could be found in the local inflammatory exudate

O T SCHULTZ

CHANGES IN THE VERTEBRAL COLUMN OF THE NEW-BORN INFANT IN CHONDRODYSTROPHIA F KNOTZKE, Beitr z path Anat u z allg Path **81** 547, 1929

Older writers, on the basis of gross examination, described lordosis and kyphosis as the only changes shown by the vertebral column in chondrodystrophia Later observers have reported histologic alterations in the bodies and laminae of the vertebrae almost as marked as those of the long bones In spite of such alterations the vertebral column, except for such lordosis or kyphosis as may be present, is usually as long as that of a normal adult Seeking to find an explanation of this fact, Knotzke made a comparative study of the long bones, the vertebral column and the cranial bones of a normal, full-term, new-born infant and of a full-term, new-born chondrodystrophic infant He concludes that chondrodystrophia is a disturbance, not of cartilage formation, but of enchondral bone formation The changes characteristic of the disease are therefore greatest in the bones laid down primarily as cartilage, namely, the long bones and those of the base of the skull, and least in other bones, that is, the vertebral bodies and the bones of the cranial vault The vertebral laminae are affected in the same way and to the same degree as are the long bones, shortening of the laminae resulting in a decrease of the anteroposterior diameter of the spinal canal The thickening of the periosteum at the epiphyses of the long bones is considered probably compensatory in nature Interference with the development of the ossification centers of the vertebral bodies and fibrosis of the medullary canals occur only in the direction of the long axis of the notochord, not in all directions as in the long bones, hence the degree of deformation of the vertebral bodies is relatively slight In the epiphyses of the long bones, as in the bodies of the vertebrae, endochondral bone formation runs a more normal course than in the shafts of the long bones, the epiphyses therefore reveal a relatively lesser decrease in size than do the shafts of the long bones

O T SCHULTZ

HAIRY POLYP OF PHARYNX A FELLER Beitr z path Anat u z allg Path **81** 658, 1929

Feller describes a pharyngeal hairy polyp obtained from a stillborn, full term infant The tumor was the size of a hen's egg and was attached at the posterior portion of the hard palate and the vault of the pharynx by a broad base It was

covered by skin and by a growth of fine hairs. On microscopic examination, it was found to contain well differentiated derivatives of the three germinal layers. The structure was organoid in character, a teratoma and not an embryoma. The author places the tumor in group III of Schwalbe's classification of the epignathus. In accordance with this classification, the author derives the structure from a totipotent misplaced blastomere.

O T SCHULTZ

BILATERAL DUCTUS ARTERIOSUS G SALZER, Beitr z path Anat u z allg Path **81** 671, 1929

In an infant, a girl, who died at the age of 7 weeks, a diagnosis of congenital heart disease had been made shortly after birth. She had been cyanotic from birth. The patient was admitted to the hospital at the age of 1 month for infectious pemphigus. The area of cardiac dulness was increased, and the second aortic sound was intensified. The cyanosis became gradually more intense, and the child died in spite of improvement in the infectious condition of the skin. The clinical diagnosis was congenital heart disease, probably transposition of the arterial trunks. At necropsy the heart was found greatly enlarged. It consisted of a single ventricular chamber and a single auricular chamber. Nothing suggestive of a rudimentary ventricular septum could be found. In the auricle was a small ridge which was thought to be probably part of the lower boundary of the foramen ovale. The trunk of the pulmonary artery was obliterated. A persistent ductus botalli united the right pulmonary artery with the arch of the aorta, and a similar structure united the left pulmonary artery with the aorta at the level of origin of the left subclavian artery. The anomaly is considered a maldevelopment resulting from inhibition of growth (*Hemmungsmisbildung*), the inhibition manifesting itself in failure of the formation of the cardiac septums and in failure of the normal regression of the gill cleft arteries.

O T SCHULTZ

HISTOGENESIS OF THE INFLAMMATORY REACTION A A MAXIMOW, Beitr z path Anat u z allg Path **82** 1, 1929

This paper, the last from the pen of Maximow, restates the results of a line of work on which he had been engaged since 1902 and reiterates the views held as the result of that work. Although it takes into consideration all of his older work relating to the histogenesis of the inflammatory reaction, it is based also on new experimental studies of the inflammatory reaction of the subcutaneous tissue of the rat, undertaken with the aim of testing the validity of the contentions of the von Mollendorfs relative to the origin of inflammatory exudate cells. In the normal subcutaneous areolar tissue of the rat, Maximow recognizes, in addition to mast cells and fat cells, only three types of cells, fibroblasts, resting wandering cells or histiocytes and eosinophilous leukocytes, the latter being distinct from the granular leukocytes of the blood. Under the influence of an inflammatory stimulus, granular leukocytes, lymphocytes and monocytes invade the tissue from the blood stream, and the local histiocytes become transformed into ameboid, phagocytic polyblasts, as do also the lymphocytes which have emigrated from the blood. The origin, transformations and fate of the hematogenous granular leukocytes, the fibroblasts and the polyblasts are described, greatest attention being given to the polyblasts. The contribution is an evaluation of results obtained by the use of careful histologic technic and of conclusions reached by the mode of thought of the anatomist, as compared with the results obtained by the vital, supravital, physical, chemical and physicochemical methods of the modern experimental pathologist and of the mode of thought of "Pathologen und Kliniker." It is a scathing criticism of what Maximow considered to be poor technical methods. It is a caustic criticism of the conclusions reached by others by means of improper technic. It is a sarcastic criticism of the work of those who have apparently entirely neglected or overlooked his own previous work. It is a polemic against von Mollendorf and his school, who ascribe

embryonic multiple potencies to what they term the fibroblastic syncytium, which may give rise to all the various types of cells present in an inflamed tissue. It is the cry of a man who felt that his life's work had not been appreciated. This feeling is suggested in Maximow's maximum in his opening paragraph, "Es wird aber heutzutage in der Biologie und Medizin so viel geschrieben und so wenig gelesen," and is apparent in the frequent references to his own work, knowledge of which should have prevented the appearance of much that has been published. Maximow was a master of several languages and could express himself equally well in all of them, he seemed to know the idiom of the language in which he wrote. Certainly no German ever used his own language more bitingly and more incisively, yet withal more precisely, than did Maximow in his last contribution. It is published as left by him, in the form of his first draft. Perhaps if he had lived he would have softened its tone somewhat, which would have been unfortunate. It is an excellent summary of Maximow's work and views in a field to which he devoted much of the energy of a lifetime. The article opens with an introduction by Maximow's pupil, colleague and friend, William Bloom, who describes the circumstances under which the manuscript was prepared. It closes with a short paragraph by Maximow's colleague and friend, Ludwig Aschoff, who regrets that Maximow had the feeling that his own work was not properly appreciated by German pathologists. There are thirteen plates excellently reproduced in halftone.

O T SCHULTZ

SENILE FIBROSIS L MULLER, Beitr z path Anat u z allg Path 82 57, 1929

Senile fibrosis is defined by Muller as an increase in the fibrous framework of the parenchymatous organs of the body. If such a process occurs it must be a physiologic manifestation of advancing age, and all other factors such as inflammation, degeneration and venous stasis must be excluded. To determine whether there actually is such a thing as senile fibrosis, he made a comparative study of the framework of various organs and tissues of persons of various ages. Paraffin sections of uniform thickness were subjected to trypsin digestion and were stained and the framework was studied. As the result of such study he divides the supporting framework of tissues and organs into a reticulum fiber system, which occurs in the spleen, lymph nodes and liver, and a basal membrane system, which occurs in adipose tissue, skeletal muscle, myocardium, suprarenal glands, thyroid gland, hypophysis, kidney and lung. The first, which is composed of a meshwork of fibrils, corresponds to what has been called the reticulum of the organs in which it occurs. The second, composed of a meshwork of flattened, membrane-like fibers, is more extensive than the gutter fibril system of the tissues in which it occurs. The framework is considered a homogeneous transformation of the embryonic mesenchymal ground substance. Collagen is not present in it, except in the broader supporting bands which separate lobules or lobes and in the capsules of organs. The framework described by Muller does not increase with age, either relatively or absolutely. On the contrary, with age there occurs a progressive decrease in the supporting framework which runs parallel with the disappearance of parenchymatous elements. A relative thickening of the capsule and septums occurs as the result of senile atrophy of the organs. Muller concludes that there is no true senile fibrosis.

O T SCHULTZ

TRANSFORMATION OF EMIGRATED LYMPHOCYTES INTO POLYBLASTS IN THE INFLAMMATORY REACTION A KARMALLY, Beitr z path Anat u z allg Path 82 92, 1929

In the number of Ziegler's *Beitrage* that contains Maximow's last word on the polyblast theory, appears this brief report, based on work done in Aschoff's laboratory, of results which are interpreted as diametrically opposed to Maximow's repeated assertion that emigrated lymphocytes become transformed into polyblasts in the field of inflammation. Before reading this article, one should

read, in the original, what Maximow has to say about technical methods. Karmally believes that many of the emigrated mononuclear blood cells that Maximow held to be lymphocytes were probably monocytes. He substantiated this belief by the use of the supravital staining method, by means of which he claims that it is easy to distinguish between the lymphocytes and the monocytes of the rat's blood. He set up inflammatory reactions in the skin and in the peritoneal cavity of normal rats and of rats which had been treated with benzene or with the roentgen rays. In normal animals, emigrated leukocytes and monocytes predominate in the inflammatory area, the histiocytes take part in the reaction only secondarily and later. In animals treated with benzene, emigration of leukocytes and monocytes is slight, and the histiocytic reaction predominates. The cellular composition of the inflammatory tissue of rats treated with the roentgen rays is intermediate between the other two. In the inflammatory peritoneal exudate of rats receiving preliminary treatment with benzene or the roentgen rays, leukocytes predominate and lymphocytic emigration is slight. Gradually the monocytes (histiocytes) become more numerous and the lymphocytes become correspondingly fewer. In preparations of the blood and peritoneal exudate that were incubated, a transformation of lymphocytes into monocytes could not be observed. Karmally admits the transformation of monocytes into polyblasts, but denies the transformation of lymphocytes into monocytes or polyblasts.

O T SCHULTZ

SIGNIFICANCE OF FINELY GRANULAR CALCIUM IN THE ARTERIAL MEDIA E
FARKAS and P FASAL, Beitr z path Anat u z allg Path 82 102, 1929

A systematic study of the presence of finely granular calcium in the media of the arterial system was undertaken by the authors for the purpose of determining a possible relation of this process to arteriosclerosis and atherosclerosis. Deposition of finely granular calcium in the media was encountered so frequently in persons of 20 years of age and over as to appear almost physiologic. The quantity of the deposit increases with age. It bears no apparent relationship to any disease. In arteries that showed no change other than the presence of finely granular calcium in the media, the percentage distribution of the process for the various arteries examined was as follows: coronary, 9 per cent; renal, 11 per cent; radial, 21 per cent; femoral, 39 per cent; aorta, 83 per cent. In cases with fibrous thickening of the intima (arteriosclerosis), the percentage distribution was as follows: coronary, 4 per cent; renal, 20 per cent; radial, 65 per cent; femoral, 75 per cent; aorta, 83 per cent. In cases with true medial calcification (atherosclerosis), the figures were as follows: coronary, 25 per cent; renal, 35 per cent; radial, 75 per cent; femoral, 82 per cent; aorta, 95 per cent. Although the process is relatively somewhat more frequent in arteries which are the seat of atherosclerosis, the authors do not think that the presence of finely granular calcium in the media bears any causal relationship to atherosclerosis. The process is the result of the functional demands made on the vessel wall and is the result of physiologic wear and tear of the arterial tissues.

O T SCHULTZ

EFFECT OF EXPERIMENTAL OCCLUSION OF THE RENAL VEIN R NISHII, Beitr z
path Anat u z allg Path 82 112, 1929

Thrombotic occlusion of the renal vein in the human being has variable effects, sometimes slight, sometimes grave, depending on the rapidity with which the occlusion occurs. If this is gradual, a good collateral circulation is developed and the effects are slight. It has been claimed by several workers that a collateral circulation is not readily developed in the rabbit after occlusion of the renal vein, this animal differing in this respect from the human being and the dog. Nishii repeated such experiments and attempted also to bring about a gradual narrowing of the vein with final complete occlusion. Sudden complete stoppage of the venous outflow led to necrosis of the kidney that was complete except for small areas near the hilum. The kidney underwent fibrous contraction, calcification and even

bone formation. If the hindrance to the outflow was more gradually brought about, little change occurred so long as any outflow was possible. The final complete occlusion of a renal vein which had been narrowed by previous procedures resulted in necrosis of the kidney. In one such experiment, however, a collateral circulation developed and little damage was done to the kidney by the final closure of the vein. Nishii concludes, in agreement with others, that the degree of injury following occlusion of the renal vein depends on the degree to which a collateral circulation is developed, and that in the rabbit an adequate collateral circulation is not readily formed.

O T SCHULTZ

ARTERIAL CHANGES IN SPONTANEOUS GANGRENE K SPONHEIMER, Beitr z path Anat u z allg Path **82** 122, 1929

The author criticizes the modern tendency in pathology which makes functional changes predominant and morphologic alterations secondary. He feels that this tendency manifests itself in discussions relating to the pathology of the vascular system, in which vasomotor changes are held responsible by some for all the anatomic alterations encountered. As a contribution to the subject he presents two cases of gangrene of an extremity. In the first case, that of a man, aged 28, the vascular lesion was a typical thrombo-angitis obliterans. The author accepts and presents Buerger's conceptions of this disease in great detail. The second case was one of gangrene of the left foot in a man, aged 38, with recurrent polyarthritis and a fresh rheumatic endocarditis on the basis of an older rheumatic valvular lesion. The vessels of the extremities, both upper and lower, were greatly thickened and their lumen was diminished. No details of microscopic observations in the second case are presented.

O T SCHULTZ

THE PRESENCE OF FIBRIN IN THE TUBERCLE K EVELBAUER, Beitr z path Anat u z allg Path **82** 141, 1929

Following a general discussion of exudative inflammatory reactions in the tubercle, the author describes the localization and morphology of fibrin in the early tubercles present in the liver and spleen in three cases of chronic pulmonary tuberculosis with cavity formation and caseous pneumonia. He found the Eppinger method for demonstrating bile canaliculi the best staining method for fibrin in the tissues. He made two slight modifications in the Eppinger method. After mordanting of the block of tissue, sections were cut on the freezing microtome instead of in celloidin, and the hematoxylin solution was allowed to act for twenty-four hours at incubator temperature instead of from one-half to several hours as in the original method.

O T SCHULTZ

CARDIAC MALDEVELOPMENTS IN ADULTS H G SCHRAMM, Beitr z path Anat u z allg Path **82** 153 1929

Two cardiac anomalies of types usually considered incompatible with a long duration of life are described. In a man, aged 48, the aorta arose to the right of and behind the pulmonary artery, being situated between the latter and the right auricular appendage. There was a subaortic defect of the ventricular septum. This heart is considered an example of Spitzer's type 1 of transposition. In a second case, that of a man aged 58, both the aorta and the pulmonary artery arose from the right ventricle, the ventricular septum being defective. This is Spitzer's type 2 of transposition.

O T SCHULTZ

RACEMOSE ANGIOMA OF BRAIN WITH VARIIX FORMATION AND RUPTURE A RUHL, Beitr z path Anat u z allg Path **82** 163, 1929

A man, aged 32, became suddenly ill with symptoms of cerebral irritation, nausea, vomiting, opisthotonos, stiffness of the neck, a positive Kernig sign and loss of consciousness. Consciousness returned the next day but the patient

remained in a semi-irrational condition. The temperature was normal. On admission to the hospital on the eighth day, papilledema and multiple retinal hemorrhages of the left eye were noted. The cerebrospinal fluid was under greatly increased pressure and was yellowish. Death occurred on the sixteenth day. At necropsy clotted blood was present at the base of the brain and between the cerebellum and the occipital lobes. The lateral ventricles were dilated by partly clotted blood. In the region of the left side of the brain stem and causing an elevation of the floor of the left lateral ventricle was a hemorrhagic tumor mass the size of a hen's egg. Macroscopically, two varices the size of a cherry could be detected. Rupture of both of these had occurred. Microscopically, the mass was a venous racemose angioma. Previously reported similar cases, which are few in number are briefly reviewed.

O T SCHULTZ

ATRESIA OF THE AORTA IN AN ADULT K. DECKNER, Beitr z path Anat u z allg Path 82 172, 1929

In a woman, aged 70, the aorta was found obliterated at the level of attachment of the obliterated ductus arteriosus. An adequate collateral circulation had been formed by way of the deep cervical, lateral thoracic, internal mammary, intercostal and inferior epigastric arteries. Terminal thrombosis had occurred in some of these collateral vessels and in the aorta below the point of atresia. Atresia of the aorta at the level of the ductus arteriosus is not a rare anomaly in the new-born but is usually not compatible with a long duration of life. The author could find twenty examples of the lesion in the literature. He expresses his belief that the effects of the lesion are slight if the obliteration of the ductus and of the aorta occur so gradually that there is time for the development of a collateral circulation.

O T SCHULTZ

ANTHRACOTIC CAVITY FORMATION IN THE LUNG G. STERN, Beitr z path Anat u z allg Path 82 178, 1929

The older literature contains many references to cavity formation in the lung which was considered to be the result of anthracosis. In England the condition was known as black phthisis, in Germany as phthisis atra, and in France as phthisie charbonneuse. More exact knowledge of the tuberculous process established that most of these cases were examples of cavity formation due to tuberculosis. Anthracosis came to be looked on as a relatively harmless process, although silicosis was known to cause marked changes in the lung. In the later literature, instances of nontuberculous cavity formation in anthracotic lungs are few. The author presents such a case. The formation of the multiple cavities noted is ascribed to degeneration, necrosis and softening of chronically inflamed tissue, the vascular supply of which becomes inadequate for proper nutrition of the tissue. The following percentages of some of the constituents are of interest: normal lung dried substance, 16 per cent, ash 4.5 per cent of dried substance; coal dust 0.6 per cent, silicate dust 0.2 per cent; anthracotic lung with cavity formation dried substance 20 per cent, ash 8.5 per cent of dried substance, coal dust 12.6 per cent, silicate dust 1.6 per cent. In view of the comparative innocuousness of coal dust in the lung, the author believes that the increased silicate content is an important factor in determining the formation of cavities.

O T SCHULTZ

MALDEVELOPMENTS OF THE LUNG F. ALTMANN, Beitr z path Anat u z allg Path 82 199, 1929

On the basis of thirteen examples, most of them in new-born infants or still-born fetuses, Altmann makes a classification of maldevelopments of the lung into which he thinks most, if not all of the previously described examples can be fitted. The maldevelopments are divided into two main groups: those characterized by disturbances of growth, and those characterized by failure of develop-

ment of the epithelial or mesenchymal element in a circumscribed area with overgrowth of the other element. Cyst formation may occur in either group. The first group is subdivided into two groups. In one there is simple overgrowth of the bronchi and their end branches. This process may involve a restricted area or a whole lobe or lung. The bronchial overgrowth may be associated with varying degrees of incomplete differentiation. In the second subgroup there is localized overgrowth of the bronchial branches, with a failure of development of the terminal outgrowths of the bronchi. In the second main group the process is one of hyperplastic or blastomatous overgrowth in a localized area of elements normally present, but because of the proliferation of one or the other element, the relationship of the tissue elements to each other is an abnormal one. The second main group is subdivided into two subgroups, depending on whether the epithelial or mesenchymal elements are hyperplastic. Two examples of mediastinal cyst are included, these the author is also able to place in his classification.

O T SCHULTZ

HISTOLOGY OF CEPHALHEMATOMA O HATSCHKE, Beitr z path Anat u z allg Path 82 268, 1929

Hatschek says that the histology of the reparative changes in cephalhematoma has not been previously described. He presents in detail a microscopic study of the process based on two examples. The first came from a child which lived seventeen days, the second from one which lived three months. In each case there was congenital internal hydrocephalus. In the first case there was an external and an internal hematoma, in the second case, only an internal one. In the first case, the bone between the central portions of the two hematomas was necrotic. Organization of the hematoma occurs at the periphery by the formation of cellular connective tissue. The pericranium or the dura, lifted off by the hemorrhage, acts as a cambium layer and forms new bone in the organization tissue. Toward the central portion, away from the lateral margins, the area of hemorrhage had become encapsulated by a thin layer of dense fibrous tissue. Connective tissue proliferation was no longer active in this tissue, but new bone formation was in process, both above and below the encapsulated hemorrhage. Red blood corpuscles had disappeared from the latter. The author believes that the hematoma must finally be replaced by new formed bone, which forms a layer considerably thicker than the normal skull. Although he has not seen the still later stages, he believes that the thick layer of new formed bone is gradually reduced to normal thickness by pressure exerted on its inner surface by the growing brain. He appends a description of the proliferative changes and new bone formation in a syphilitic cranial osteophyte into which hemorrhage had occurred at birth.

O T SCHULTZ

APLASIA OF THE THYROID IN RELATION TO ENDOCRINE FUNCTION DURING FETAL LIFE E J KRAUS, Beitr z path Anat u z allg Path 82 291, 1929

In his discussion of the question whether the endocrine organs manifest their specific functions during fetal life, Kraus quotes the opinion of E J Thomas that these organs exhibit no activity during the fetal period under normal conditions, but that the fetus is dependent for its endocrine hormones on those of the maternal circulation. As a contribution to this question, he presents a study of a male infant 47 cm long, which died on the day of birth. In addition to multiple anatomic maldevelopments, the following changes were noted in the endocrine system: complete aplasia of the thyroid, hypoplasia of the thymus, hyperplasia of the hypophysis and suprarenals. The parathyroids, the interstitial cells of the testes, and the islands of Langerhans were normal. The hypoplastic thymus revealed microscopic evidence of involution. The hyperplasia of the hypophysis involved the anterior lobe and was due to an increase in the number of large chromophobe cells. Both the cortex and medulla of the suprarenals

were hyperplastic and the medulla gave the chrome reaction, which is accepted as evidence of epinephrine formation. Kraus interprets the changes noted in the endocrine system as proof that a mutual inter-relationship of the organs of this system exists during fetal life and that the endocrine system functions specifically before birth.

O T SCHULTZ

THE MARROW OF THE HUMAN FEMUR W. HALLERMANN, Beitr z path Anat u z allg Path **82** 345, 1929

Although much attention has been paid to changes in the marrow which manifest themselves in alterations of the cellular composition of the circulating blood, little attention has been given, according to Hallermann, to changes in the marrow that do not lead to deviations from the normal blood picture. His report is based on the study of the marrow of the femur of 1,400 necropsies made during a period of about eight months in Schmorl's institute, where the right femur is routinely removed for examination, in many cases the left femur was also removed. A frontal section of the bone permitted examination of the marrow from the head of the condyles. Hallermann's study was directed along three lines: the relative distribution of red and fatty marrow in the femur, localized changes in the femur marrow without alterations in the peripheral blood and changes peculiar to the fatty marrow alone. Red marrow was found to be present in most of the femurs examined, being usually limited to the upper third of the bone. It occurred as small islands in the fatty marrow, as a narrow zone immediately beneath the cortical layer of the bone, in the neck of the femur as a red streak in the long axis of the bone or as a layer beneath the cartilage of the head. The localized changes noted were hemorrhages into the marrow, cyst formation, and necrosis. Localized hemorrhages were seen in forty cases and cysts in fourteen. The lesion to which the author devotes most attention is one limited to the fatty marrow, often visible in the gross as a yellow zone about an older area of hemorrhage. Microscopically, such areas were composed of necrotic fat cells and of new formed cells which contained fat droplets. The necrosis, which was often associated with fibrin formation, is held to be due to poor nutrition of fat cells about areas into which hemorrhage has occurred. The new formed cells containing fat, the author believes to be reticulum cells which have stored the fat liberated by necrotic fat cells. He does not consider them true fat cells or lipoblasts, and their formation is not a process of regeneration of true fatty marrow.

O T SCHULTZ

PRIMARY ARTERIOSCLEROSIS OF THE PULMONARY ARTERY U. STEINBERG, Beitr z path Anat u z allg Path **82** 443, 1929

In this communication Steinberg, who had discussed the subject of secondary pulmonary arteriosclerosis in the preceding number of the *Beilage*, reports two cases of the primary form of the condition. The patient in one was a man aged 50, the other was a woman aged 52 years. The man had had an attack of acute rheumatic polyarthritis a year before his death. In each case a clinical diagnosis of valvular disease of the heart had been made. Common to both cases was marked hypertrophy of the right ventricle, and slight macroscopic arteriosclerosis of the larger pulmonary vessels and general circulation. In the first case the smaller arteries and arterioles of the lung were the seat of a marked and widespread productive inflammatory process, which was most marked in the adventitia and had led to great narrowing of the lumen. The process is held to have been infectious in origin and probably rheumatic. In the second case the small arteries and arterioles were involved in an arteriosclerotic process which was characterized by intimal thickening that greatly decreased the lumen. The hypertrophy of the right ventricle was ascribed in each case to the mechanical hindrance to the pulmonary circulation offered by the narrowing of the arterioles. In each case many of the vessels were thrombosed.

O T SCHULTZ

ACUTE PEPTIC GASTRITIS E HAMMER, Beitr z path Anat u z allg Path
82 485, 1929

As a contribution to the much discussed question as to whether the gastric juice can injure the previously normal mucosa, as Aschoff and his pupils have maintained, or can exert its digesting action on the mucosa only after the latter has been already damaged, as most others have contended, Hammer presents a study of a process which he terms acute peptic gastritis. To obtain material for study, stomachs removed at necropsy done immediately after death were fixed at once and subjected to serial microscopic examination. In four stomachs with acute macroscopic ulcers in the pyloric region and in one with a similar lesion in the duodenum, the mucosa contained multiple microscopic lesions which are described in detail. These were usually situated in the deepest parts of the furrows, and in all but one case they were limited to the pyloric region. The lesions, which rarely penetrated deeper than the upper third of the mucosa, consisted of a superficial zone of fibrinoid hyaline necrosis. At the margin this zone was covered by the surface epithelium, at the center the latter was absent. Some of the capillaries within the zone of necrosis contained hyaline thrombi. About the area of necrosis was a zone of leukocytic infiltration, in which fibrin was sometimes present. The capillaries in this zone were not thrombosed, but contained an increased number of leukocytes. The process is interpreted as an inflammatory reaction in a previously undamaged mucosa, the reaction being brought about by the caustic action of the gastric juice on the living tissue. The explanation of the focal character of the lesions offers difficulties. Hammer suggests that during contractions of the stomach, the gastric juice may be held for longer periods within the furrows of the mucosa. Other factors may have a part in rendering the mucosa subject to the action of the gastric juice, but the author contends that the acute inflammatory reaction is the result of the direct and primary action of the gastric juice on the tissue.

O T SCHULTZ

ATHEROSCLEROSIS OF THE CORONARY ARTERIES OF THE HEART KAPITOLINE
WOLKOFF, Beitr z path Anat u z allg Path 82 555, 1929

Under arteriosclerosis are included a number of processes, one of which is atherosclerosis. By atherosclerosis the author understands a condition characterized by lipid infiltration of the deepest layer of the intima, by fibrous thickening of the intima over the area of infiltration, and by the formation of nodular plaques that contain lipoids, chiefly cholesterol or its esters, and that protrude into the lumen of the vessel. Previous studies of atherosclerosis of the coronary arteries have been chiefly statistical in character. The author made a systematic macroscopic and microscopic study of the coronary arteries of 120 persons ranging in age from 4 months to 75 years, with a fairly even distribution among the different decades. There were fifteen cases in each of the first six decades except the first, in which there were twenty, and the fifth and sixth, in each of which there were sixteen, there were fourteen cases in which the patients were more than 60 years of age. The normal functional and histologic characteristics of the coronary arteries differ from those of any other part of the arterial system. The coronary circuit is a short one and is the first one to be given off from the aorta, hence it is subjected to a higher intra-arterial pressure than exists elsewhere. This functional characteristic manifests itself by a physiologic increase of elastic tissue in the intima, to such a degree that by the second or third decade the intima is as thick as the media, a normal structure exhibited by no other artery. Atherosclerotic changes begin to make their appearance in the coronary arteries during the first decade of life and increase in frequency with each succeeding decade. In the series studied they were noted in 2 of 20 cases of the first decade, in 9 of 15 cases of the second decade, in 12 of 15 cases

of the third decade, in 13 of 15 cases of the fourth decade and in every case of all later age periods. In the earlier periods of life they occurred in the main trunks of the coronary arteries and consisted only of flecklike areas of lipid infiltration. With increasing age, the process progressively involved the rest of the coronary system, the left coronary almost without exception being involved to a greater degree than the right. At about the middle of the second decade, fibrous thickening of the intima over the areas of infiltration makes its appearance and becomes progressively more marked at later ages. Nodular atherosclerotic plaques begin to appear during the fourth decade, these in their turn become progressively more numerous as the age increases. The progressive increase in the incidence of atherosclerotic changes, and the appearance of fibrous thickenings and of nodular plaques as the age increases indicate, as does also the histology of the lesions that the three types of lesions, that is, pure lipid infiltration, thickening of the intima, and the formation of atherosclerotic plaques, are progressive stages of a single process. The primary condition in this process is lipid infiltration, as postulated by Anitschkow, in whose laboratory the work was done. Thickening of the intima and plaque formation are secondary reactions to the infiltration. The plaques as a rule contained much lipid material. In a few instances, the plaques contained little or no lipid. In such lesions there was noted an ingrowth of capillaries into the plaque from the media. The capillaries were surrounded by xanthoma cells. Resorption of lipid material from the plaques may therefore occur. The regressive changes seen in the plaques were crystallization of cholesterol, atheromatous softening and calcification. The most important general factor in atherosclerosis is the abnormality of metabolism which leads to lipid infiltration. A second general factor is the increased arterial pressure. Local factors which influence the frequency and distribution of the process in the coronary arteries are the relatively higher pressure in the coronary circuit and the structure of the coronary arteries.

O T SCHULTZ

CHOLESTEROL PERICARDITIS H. HERZENBERG and I. FATH-GORDON,
Centralbl f allg Path u path Anat 46 97, 1929

Autopsy of the body of a 21 year old woman disclosed a scirrhus carcinoma of the stomach and a bronchiogenic carcinoma of the left upper lobe with extensive metastases. The left pleural cavity contained about 250 cc and the pericardial sac about 750 cc of a yellow fluid. The epicardium contained metastases and in addition warty yellow growths and granulations. Presumably the authors encountered a case of Hydrops adiposus seu chyliformis, because analyses of the pericardial fluid yielded 7 per cent albumin and 55 per cent cholesterol. The carcinoma metastases had invaded all layers of the epicardium and blocked the lymphatic drainage.

GEORGE RUKSTINAT

SCLEROSIS OF MULTIPLE ENDOCRINE GLANDS P. F. RICHTER, Deutsche med Wchnschr 55 1760, 1929

In a woman, aged 62, in whom axillary and pubic hair and eyebrows had fallen out thirty years before, there was noted increasing muscular weakness, slow scanning speech and apathy for two years. Shortly before death there were alternating periods of unconsciousness and consciousness. The essential clinical signs were a marked secondary anemia, a systolic blood pressure of 85 and a basal metabolic rate of less than normal. The postmortem examination disclosed a marked atrophy of the hypophysis, thyroid gland, suprarenal glands and ovaries. Histologically there were marked fibrous changes and atrophy of these tissues. It was thought that a puerperal infection thirty years previously might have initiated these changes.

PAUL J. BRESLICH

ARTERIAL CHANGES IN POISONING WITH IRRADIATED ERGOSTEROL (VIOSTEROL)
R. HUCKEL and H. WENZEL, *Ztschr f Kreislaufforsch* **21** 409, 1929

Viosterol was given to rabbits by mouth in amounts of from 9 to 700 mg within from one to three weeks, in single doses of from 1 to 100 mg. The animals lost weight and nearly all of them died spontaneously. Macroscopic examination of the arteries of rabbits which had not received more than a total dose of 20 mg revealed elevations in the beginning of the aorta. In animals which had received from 50 to 70 mg of viosterol the ascending portion of the aorta was thickened and its inner surface was rough and contained hard plaques that projected into its lumen. In the descending portion of the aorta the changes were less marked but at the transition from the thoracic aorta to the abdominal aorta they were pronounced, the lower lumbar portion of the aorta was macroscopically free from changes. In animals which had received from 100 to 200 mg of viosterol the process involved the entire aorta. In all the animals which had received still larger doses the whole aorta had been converted into a rigid tube which curled outward when incised longitudinally. The extensive, hard deposits of calcium with intervening large and small aneurysms and the rough inner surface of the aorta constituted a characteristic picture of the vascular injuries produced by viosterol. Compared with these changes in the aorta, the changes in the large arteries were unimportant. Microscopically, calcification could not be demonstrated in animals that had received a total dose of only 12 mg, in these animals, however, marked changes in the media were noted. The outer layers of the media were loosened and presented a honeycomb marking. Large vesicular cells which did not contain fat were present. The irregularity of the inner surface of the aorta was particularly marked in one animal which had received a total of 14 mg. In the projections the fibers of the media were loosened. Particularly the inner layers of the media were characterized by localized areas that stained poorly, in these areas the elastic fibers were decreased in number and showed interruptions in their continuity. In some places in the aorta structures resembling giant cells were noted, together with degeneration of the nuclei and fibers and calcification. In areas in which the calcification of the media was marked, the overlying intima had become necrosed whereas the outer layers of the media were almost unchanged. From this study it is evident that the first morphologic changes in the development of the process occur in the media. Examination of the arteries of the kidney revealed that here, also, the pathologic process began in the media. Changes in the media of the arteries of the kidney were noted in animals that had received only 9 mg of viosterol. Contrary to the changes in the aorta, large doses of viosterol produced extensive primary necrosis of the media of the arterioles of the kidney. The author emphasizes the fact that only minute quantities of viosterol were required to produce marked injury of the wall of the aorta and of the arteries of the kidney.

THE INFLUENCE OF INFECTION ON THE THYROID GLAND AND ITS SIGNIFICANCE
IN THE ETIOLOGY OF GOITER IN HOLLAND. H. L. KOESTER, Dissertation,
Utrecht, 1929

In Holland, the normal thyroid gland shows a different histologic structure according to sex, age, locality, menstruation and pregnancy (43 autopsies). The normal weight of the organ varies between 20 and 50 Gm, the average weight being 30 Gm in the adult. After the age of 50, involution of the thyroid begins. The difference between normal and goitrous thyroid gland applies to the form and size of the acini, amount and quality of the colloid and height and proliferation of the epithelium. The influence of different acute and chronic infectious diseases on the thyroid gland was studied in ninety-five autopsies. Following acute infectious diseases, typhoid fever and septicemia, the thyroid gland showed hyperemia, decrease of colloid and desquamation of the epithelial cell layer. These changes did not resemble the histologic appearances in goiter.

Bacteriologic examinations of twenty-seven goiters and of the feces of twenty goitrous patients did not support the theory that goiter is due to some local or

intestinal infection In the feces of goitrous persons, no other micro-organisms and no more parasite eggs were found than in goiter-free people

In extensive experiments on rats, broth cultures of feces from patients with goiter were fed for four months, but the animals did not develop hyperplastic changes of the thyroid gland

C A HELLWIG

Microbiology and Parasitology

THE RELATION OF MOISTURE TO THE DISTRIBUTION OF HUMAN TRICHURIS AND ASCARIS L A SPINDLER, Am J Hyg 10 476, 1929

The incidence of *Trichuris* in southwestern Virginia was found on the whole to be much lower than that of *Ascaris* However, in an area differing from those with a low incidence of *Trichuris* only in the amount of moisture in the soil (due to the abundance of shade) the incidence of *Trichuris* was not only higher (61 per cent) than that of *Ascaris* (56 per cent) but the infestations were also quite heavy

From all the information available (laboratory experiments and incidence data), it was concluded that an important factor in the differences found in the incidence of *Ascaris* and *Trichuris* in regions where habits of soil pollution seemed favorable for their spread was a difference in the moisture requirements of the eggs This was indicated by the fact that wherever the soil was kept moist on account of high rainfall or dense vegetation, the incidence of *Trichuris* was, as a rule, high, while a high incidence of *Ascaris* was found in much drier situations

JOHN PHAIR

A RAT-FLEA SURVEY OF PEIPING MARSHALL HERTIG AND TSEFANG F HUANG
Am J Hyg 10 521, 1929

In a rat-flea survey of Peiping extending throughout one year, 6,286 rats were examined *Xenopsylla cheopis* (98 per cent) and *Ceratophyllus ansus* (2 per cent) were the only rat-fleas found The average number of *Xenopsylla* per rat was 1.33 for the whole year with a maximum of 31 in August and a minimum of 0.3 in February

Peiping's freedom from bubonic plague is not to be explained by the absence of the vector, *Xenopsylla cheopis* but would seem to be partly in its geographical position and partly in the prevalence throughout most of the year of climatic conditions, notably the extreme dryness and the cold winter, unfavorable to the establishment and maintenance of plague (Brooks, 1917)

JOHN PHAIR

THE LIFE HISTORIES OF DIPHYLLOBOTHRIUM DECIPIFENS AND DIPHYLLOBOTHRIUM ERINACEI H C LI, Am J Hyg 10 527, 1929

These life histories have been studied and are presented thoroughly

JOHN PHAIR

ON THE VIRUS OF RAT ANEMIA AND ITS TRANSMISSION BY THE RAT LOUSE, POLYPLAX SPINULOSA CALISTA P ELIOT AND W W FORD, Am J Hyg 10 635, 1929

The splenectomized Wistar rat was used for the study of insect transmission of *Bartonella munit* Living lice were picked from infected stock and placed on these test animals Seven of nine rats died of anemia within from three to five days after the first appearance of *Bartonella* and eighteen to twenty-eight days after infestation with the lice One rat recovered from the first attack and died in a relapse on the thirty-third day after infestation One rat showed a prolonged recovery One attack of *Bartonella* anemia does not protect the splenectomized

rat against subsequent spontaneous or induced attacks, while in the adult normal rat with intact spleen the disease cannot be produced. The blood of sixty-two wild rats has been examined for *Bartonella munit*. Of these, fourteen showed a definite infection. Many of the wild rats examined harbored trypanosomes and leptospiras. How much these other infections contribute to the breaking down of the defense mechanism of the spleen and so to the appearance of *Bartonella munit* has not been determined.

JOHN PHAIR

CHEMICAL CHANGES IN THE GROWTH OF AVIAN TUBERCLE BACILLI ON LONG'S SYNTHETIC MEDIUM. A. G. REINTREW, S. L. BASS and T. B. JOHNSON, *Am Rev Tuberc* **20** 114, 1929.

The growth of avian tubercle bacilli was followed analytically for a period of sixteen weeks, using the methods previously described (*Am Rev Tuberc* **18** 508, 1928) for the study of human tubercle bacilli. The most striking fact revealed was the difference in the production of the substances of carbohydrate nature. The copper-reduction curve suggests that these two micro-organisms do not produce the same carbohydrate combination in the metabolism.

H. J. CORPER

CHEMICAL CHANGES FROM THE GROWTH OF TIMOTHY BACILLI ON LONG'S SYNTHETIC MEDIUM. SHAILER L. BASS and TRIST B. JOHNSON, *Am Rev Tuberc* **20** 122, 1929.

The growth of timothy bacilli was followed analytically for a period of sixteen weeks, using the methods previously described for the study of human and avian tubercle bacilli. The most striking difference between timothy bacilli and human tubercle bacilli is revealed by the analyses for reducing sugars. Timothy and avian bacilli are both characterized by the formation of sugar of low reducing powers, while the reducing power of the sugar formed in the case of human tubercle bacilli is variable and increases to a maximum. The results of analyses indicate that the same sugar combination is not functioning in all three bacterial organisms.

H. J. CORPER

A DEVELOPMENTAL CYCLE OF THE TUBERCLE BACILLUS AS REVEALED BY SINGLE-CELL STUDIES. MORTON C. KAHN, *Am Rev Tuberc* **20** 150, 1929.

With the aid of Chamber's micromanipulator, it was possible to grow single tubercle bacilli or small groups of from two to six organisms in individual droplets of Long's medium for varying periods of time. Under the experimental conditions described, the H37 strain of human tubercle bacilli did not multiply solely by simple fission but underwent a more complex type of reproduction consisting of (a) the initial segmenting of the rod into three or more ovoid units, (b) the division of these units into diplococcoid forms, (c) subsequent grouping and reduction of these elements to a mass of dust fine particles from which extremely small and delicate rods were found to sprout, and (d) the later development of these tiny rods into the mature tubercle bacillus. A so-called "wild" strain of tubercle bacillus from urine was found to undergo an identical developmental process. Some of the stages of growth were found to be nonacid-fast. The possible relation of the forms encountered to those previously described by other observers is discussed.

H. J. CORPER

THE TISSUE REACTIONS TO PRIMARY INFECTION AND REINFECTION WITH THE TUBERCLE BACILLUS. LEROY U. GARDNER, *Am Rev Tuberc* **20** 201, 1929.

Histologic study serves as a qualitative basis for comparing the effects of primary infection and reinfection with the tubercle bacillus in the peritoneal

cavity It demonstrates that the subperitoneal tissues are not exceptional in their behavior, and that these tissues also meet primary infection with a slow proliferation, and reinfection with an inflammation accompanied by accelerated proliferation Both sensitized and nonsensitized animals respond immediately to the injection of tubercle bacilli with an acute inflammation But in the primary infection, this reaction is nonspecific and it completely disappears after forty-eight hours In the reinfection the nonspecific exudation is accentuated by hypersensitiveness, and inflammatory phenomena do not disappear, but continue with increasing severity throughout the course of the disease

H J CORFEE

CULTURING BOVINE TUBERCLE BACILLI MAX EVANOFF and H C SWFANY, Am Rev Tuberc **20** 227, 1929

A direct method is described for obtaining growths and identifying tubercle bacilli from bovine material The bovine bacilli isolated grow directly on a cream-egg-milk medium, but not on a glycerol-egg-milk medium or other glycerol-egg medium There appears to be a shower of organisms associated in the lesions of cattle that resemble paratubercle bacilli, some of which appear to be tuberculogenic after animal passage Direct inoculation and treatment with 3 per cent hydrochloric acid and 3 per cent sodium hydroxide are recommended for the best results

H J CORFEE

THE EFFECT OF ULTRAVIOLET LIGHT ON CORNEAL TUBERCULOSIS IN RABBITS H F NEWTON, Arch Surg **18** 1542, 1929

When tubercle bacilli are injected into the cornea and it is then exposed to ultraviolet irradiations before it shows a gross tuberculous lesion, the bacilli are destroyed and corneal tuberculosis is prevented On the other hand, if the lesion has developed, ultraviolet irradiation does not sterilize the cornea, and even accelerates the ulceration and exudate

N ENZER

THE AGENT OF HERPES HANS ZINSSER and FFI-FANG TANG, J Immunol **17** 343, 1929

The virus deteriorates rapidly in the presence of free oxygen, but survives for considerably longer periods under anaerobic conditions The presence of serum also favors survival of the virus The serum of convalescents from encephalitis may neutralize herpes virus, this action of serum is independent of complement Efforts to immunize with the dead herpes agent failed entirely

OBSERVATIONS FOLLOWING THE FEEDING OF SALMONELLA ENTERITIDIS TO RATS ON DIETS VARYING IN VITAMIN A CONTENT ELIZABETH VERDER, J Prev Med **3** 489, 1929

Two of nine rats on a diet containing an adequate amount of vitamin A developed a profuse watery diarrhea from twelve to twenty-four hours after swallowing a suspension of living *S enteritidis*, while none of the ten rats on diets containing very small amounts of this vitamin showed any symptoms of "food-poisoning" In this series of experiments neither the ability of this strain of *S enteritidis* to invade the tissue nor its capacity to persist and probably increase in numbers in the duodenum were of importance in provoking "food-poisoning" symptoms The cultures of the spleen, livers, lungs, kidneys and heart blood of the rats on deficient diets showed that most of them were harboring organisms commonly found in the intestinal flora, while the organs of the rats on adequate diets proved sterile *S enteritidis* was isolated from the spleen, livers, lungs and kidneys, as well as from the duodenum, of many of the deficient-diet to which this organism has been fed

AUTHOR'S SUMMARY

BOTULISM RESULTING FROM CONSUMPTION OF CANNED ONIONS STEWART A KOSER and DOROTHY O REITFR, J Prev Med 3 499, 1929

An outbreak of botulism involving two cases with one death in Chicago in 1929 was caused by Italian canned onions (shallots) Botulinum toxin, type B, was demonstrated in the blood serum but not in the spinal fluid in the fatal case The presence of *Clostridium botulinum*, type B, was also demonstrated in the small intestine (ileum) Inspection of approximately 400 cans of the same shipment revealed slightly over 1 per cent of swelled cans One swelled can, secured from a retail store, was found to be toxic and a culture of *Clostridium botulinum*, type B, was isolated from this

AUTHORS' SUMMARY

QUAIL AS A POSSIBLE SOURCE OF TULARAEMIA INFECTION IN MAN R R PARKER, Pub Health Rep 44 999, 1929

Quail should be considered at least potential agents of human infection with tularemia

AUTHOR'S SUMMARY

THE NATURE OF THE LESIONS IN GENERALIZED VACCINIA IN RABBITS JAMES MCINTOSH and R W SCARFT, J Path & Bact 32 551, 1929

With certain strains of virus, generalized vaccinia in rabbits regularly occurs, both after scarification and after intravenous inoculation All the lesions of generalized vaccinia show the histologic picture of an infective granuloma affecting primarily the smaller blood vessels with endothelial proliferation, necrosis of tissues and subsequent fibrosis The visceral lesions are due to the direct action of the vaccinia virus and not to the activation of a latent infection

AUTHORS' SUMMARY

THE EXOTOXINS OF STAPHYLOCOCCUS PYOGENES AUREUS F M BURNET, J Path & Bact 32 717, 1929

The agent obtained in staphylococcal culture filtrates that is capable of killing rabbits acutely on intravenous injection is a true exotoxin The three activities of such filtrates in causing hemolysis in vitro necrotic skin lesions on intradermal injection into rabbits and acute death of rabbits after intravenous injections are manifestations of a single antigenic substance A typical anatoxin can be obtained with full antigenic power but no toxicity and diminished hemolytic power The toxin is produced in vivo in rabbits infected with a toxigenic strain of staphylococci If rabbits are actively or passively immunized to the toxin, their survival time after intravenous injection of virulent staphylococci is increased The bearing of these observations on the pathology of human staphylococcal infections and more particularly on the fatalities at Bundaberg, Queensland, is briefly discussed

AUTHOR'S SUMMARY

EXPERIMENTS TO DETERMINE WHETHER THERE IS A FILTERABLE FORM OF THE TUBERCLE BACILLUS S R GLOYNE, R E GLOVER and A S GRIFFITH, J Path & Bact 32 775, 1929

None of the animals inoculated with filtrates showed any of the obvious signs of tuberculosis, such as enlargement of the lymphatic glands with fibrosis or caseation Tubercle bacilli were found in only one microscopic preparation, these were traced to an imperfectly cleansed scalpel which though it had been boiled for twenty minutes in strong soda solution showed traces of coagulated pus at the tip The eight guinea-pigs inoculated with apparently slightly enlarged glands or organs containing doubtful foci were free from any sign of tuberculosis when killed from 58 to 115 days later, average 88 days All the young guinea-pigs were perfectly healthy Our experiments have failed to demonstrate the existence of a filtrable form of the tubercle bacillus

AUTHORS' SUMMARY

TYPES OF TUBERCLE BACILLI IN HUMAN TUBERCULOSIS A STANLEY GRIFFITH,
J Path & Bact **32** 813, 1929

The observations and experimental investigations recorded here show that tuberculous lesions, whether produced by human or by bovine tubercle bacilli, and wherever situated, may undergo spontaneous arrest and cure

AUTHOR'S SUMMARY

THE BACTERIAL CONTENT OF THE NORMAL CORNEA ADOLF BLANK, Arch f
Ophth **122** 661, 1929

A study of the germ content of the normal cornea with relation to that of the contiguous normal conjunctiva was made. With careful technic smears were obtained from the eyes of 100 normal persons and cultures were made on blood serum. In the same manner the bulbar conjunctiva also was investigated. The cultures were examined after from twelve to twenty-four hours. (Observations for pneumococcus must be made early, for these are easily overrun by the rapidly growing staphylococcus and *B. reiosis*.)

Results were often different in the two eyes of the same subject. In only 35 per cent were results for both eyes alike. In over half of the eyes examined, the cornea and conjunctiva were alike, with few exceptions the bacteria from the cornea grew more sparsely in the culture than those from the conjunctiva.

In only seven eyes were pneumococci found on the cornea and not on the conjunctiva, hence the author could not verify Lindner's statement that pneumococci are found on the cornea alone in the greater percentage of cases. Total results were as follows: pneumococci were found in 52 per cent of the aggregate eyes examined, staphylococci, in 78 per cent, *B. reiosis*, in 66.5 per cent, diplobacilli, in 4 per cent, and *B. subtilis*, in 25 per cent. Pneumococci were especially frequent in the eyes of older persons and slightly more frequent in men than in women. In general, it must be admitted that along with staphylococci and *B. reiosis*, chain diplococci (probably for the most part belonging to the pneumococcus group) grow on the conjunctiva and frequently, perhaps always, on the normal cornea also.

CHARLES WEISS

IS A BACTERICIDAL CHEMOTHERAPY OF TUBERCULOSIS POSSIBLE? F. JESSEN,
Beitr z Klin u Tuberk **72** 184, 1929

Attempts to stain tubercle bacilli vitally in diseased rabbits failed. After repeated injections of fuchsin, some of the dye was demonstrable in the center of small necroses.

MAX PINNER

PATHOLOGY OF HUMAN TUBERCULOSIS P. SCHURMANN, Beitr z path Anat u
z allg Path **81** 568, 1929

The author presents a minute and detailed study of human tuberculosis, undertaken with the object of testing the correctness of Ranke's hypothesis that human tuberculosis always runs a cyclic course. This course is composed of three stages: a first stage of primary localization of the infection, with local growth by direct continuity, spread to the contiguous lymph nodes, and relative local allergic tissue hypersusceptibility, manifested by a proliferative reaction about the tubercles, a second stage of generalization, due to direct, lymphogenous, hematogenous and intracanalicular spread or the process, with generalized allergic tissue hypersusceptibility, manifested by an exudative inflammatory reaction about the tuberculous foci, and a third stage of relative humoral immunity, in which the lesions increase by direct growth. For the purpose of his study Schurmann examined carefully for tuberculosis 1,000 consecutive unselected bodies which came to

necropsy in Fahr's institute at Hamburg Infants under 2 months of age were not included The lungs were removed in toto, fixed by intratracheal or intravascular injection, studied roentgenographically, sectioned frontally for gross and photographic study, and the necessary microscopic preparations made This communication gives the observations in the cases in which the tuberculous process was generalized, there were fifty-seven of these cases in the series In two cases the primary focus could not be detected In forty-six the primary focus was single, and in nine multiple In 78 per cent of the forty-six cases with a single primary focus, the latter was situated in the lung, in the intestine in 17 per cent, and in the neck and the middle ear each one The anatomy of the process with reference to the various modes of spread is fully described and illustrated The author speaks of his observations as the anatomie substrate of the generalization of tuberculosis He presents no conclusions as to the correctness of the Ranke hypothesis, reserving this for a later communication, in which the cases without generalization will be discussed

O T SCHULTZ

ETIOLOGY OF LYMPHOGRANULOMATOSIS NATALIA BUSNI, *Virehows Arch f path Anat* 268 614, 1928

From the blood and organs of the patient with lymphogranuloma one and the same micro-organism is constantly obtained after inoculation of suitable culture mediums The presence of micro-organisms in the blood (in contrast to Grumbach's idea) shows no relationship with the rise in temperature As regards its morphologic properties, the micro-organism obtained is similar to the tubercle bacillus The micro-organism appears as an acid-fast bacillus only in a definite stage of its development It is possible that several observers who described different types of the causative organism have observed in reality one and the same micro-organism but under different conditions of its development and nutrition The introduction of large masses of these micro-organisms gives rise in the guinea-pig to a disease corresponding to the lymphogranulomatosis in man The presence of these micro-organisms in all the tissues of the patient makes one believe that lymphogranulomatosis is a generalized infectious disease On inoculation of guinea-pigs with cultures of organisms of lymphogranulomatosis and of tuberculosis, the structure of the two different granulomas is maintained Lymphogranulomatosis is, after all conjectures, an independent disease having no connection with tuberculosis There are (a) the difference in the course and outcome of these two diseases in man, (b) the difference in behavior of the guinea-pigs to these diseases, (c) the constant presence of micro-organisms in the blood of the lymphogranulomatous patient, and finally, the most important (d) the difference in the histologic structure of both granulomas

AUTHOR'S SUMMARY

THE RÔLE OF MIXED INFECTION IN TUBERCULOSIS J R F RASSERS, *Ztschr f Tuberk* 54 198, 1929

The tubercle bacillus requires for its growth nitrogenous protein-split products, preferably amino-acids and ammonia, it seems to be unable to utilize higher compounds, such as peptones, unless free amino-acids are present Chemical analysis of tuberculous caseous material showed that it did not contain any free amino-acids The same was true of sterile pus, experimentally produced by injections of turpentine oil into a dog Any sample of pus that contained streptococci or staphylococci contained free amino-acids It is well known that caseated tubercles contain but few tubercle bacilli, while (always secondarily infected) cavities contain large numbers It is probable that the common pyogenic organisms, by splitting proteins to free amino-acids, improve the medium for the growth of tubercle bacilli

MAX PINNER

Immunology

THE REPRODUCTION OF TUBERCULIN HYPERSENSITIVENESS IN GUINEA PIGS WITH VARIOUS PROTEIN SUBSTANCES L DIENES and E W SCHOLNHEIT, *Am Rev Tuberc* **20** 92, 1929

The conditions under which the sensitiveness is produced, the characteristics of the skin reaction, and the result of passive-transfer experiments make it very probable that protein sensitiveness with necrotic skin reactions in tuberculous guinea-pigs must be regarded as a reproduction of tuberculin sensitiveness. The conditions influencing the general tuberculin reaction are so little understood that failure to produce a similar general reaction with egg-white does not weaken the foregoing conclusion. The characteristics of the tuberculin type of sensitiveness (concerning the local reactions) are not dependent on the special properties of the antigens, but are the result of a special type of sensitization which is made possible by the influence of the tuberculous tissue. It is probable that the tuberculin type of sensitiveness is the result of antigen-antibody reaction, as it follows the antigenic specificity, and as the tuberculous tissue has great influence also on antibody production. In the study of immunity in tuberculosis the study of the influence of the lesions on the immunity response of the organism will be of great importance. Certain characteristics of anaphylactic sensitization and production of anaphylactic shock in tuberculous guinea-pigs are also described.

H J CORPER

THE PERMEABILITY OF THE RESPIRATORY TRACT TO ANTIGENS PAUL F CLARK, WILLIAM S MIDDLETON and OTIS M WILSON, *Am Rev Tuberc* **20** 106, 1929

Guinea-pigs may be actively sensitized through respiratory insufflation with a variety of antigens, including one so relatively weak in antigenic properties as old tuberculin. Passive sensitization can be produced by the appropriate use of serum from these actively sensitized animals. Circulating antibodies may be demonstrated by precipitin tests following insufflation with horse serum, a solution of crystalline egg-albumin or a solution of a crystalline protein from the brazil nut. Attempts to give the shocking dose by insufflation after sensitization by the same route produced only minor symptoms of dyspnea and restlessness. In view of the difference in species and the small amount of antigen employed it is believed that these experiments indicate the possibility of the correctness of the hypothesis that the patient in a reported case may have been sensitized by repeated exposures to a tuberculin-laden atmosphere.

H J CORPER

PROTECTIVE IMMUNIZATION WITH BCG (BACILLUS CALMETTE-GUERIN) S A PETROFF, *Am Rev Tuberc* **20** 275, 1929

Recent studies on the biology of the tubercle bacillus suggest strongly that the micro-organism is not stable and may mutate. The evolution and mutation of all micro-organisms is believed in and therefore the adoption of any method of prophylactic immunization that uses a living micro-organism is opposed. Infants that become infected with a virulent micro-organism and develop a latent tuberculosis may manifest a clinical disease later in life. At present there is not an iota of scientific evidence to show that the same thing may not occur if one infects infants with BCG, there is accredited evidence to suggest that such a catastrophe might happen. The low level of acquired resistance obtained by the implantation of living micro-organisms is all one can expect. Shall one pay the price for such a resistance by infecting the whole race? If one must use a vaccine it is believed that one composed of dead micro-organisms can accomplish as much as can be obtained with BCG.

H J CORPER

THE ANTIGENIC SUBSTANCES OF THE TUBERCLE BACILLUS L DIENES, J
Immunol **17** 85, 157 and 173, 1929

In the extracts of tubercle bacilli obtained with alcohol of different strength and with methyl alcohol, six different antigens were demonstrable. Three different protein fractions were separated from bacilli and from culture broth, they have different antigenic properties and different isoelectric points. But more than these three antigens are present in protein substances. A protein not precipitable by acids has a strong tuberculin effect and it differs in its antigenic properties from the other proteins. Antibody production is strongest with whole bacilli, antisera against living bacilli are distinct from those of killed bacilli. The relative amount of antilipoids and antiproteins varies in different batches of antisera. Both watery and alcoholic extracts stimulate antibody production, the latter antisera usually contain some antiproteins. A 75 per cent alcohol extract gives rise to two antibodies not present in immune sera prepared by whole bacilli. Certain protein fractions produced precipitins against the specific carbohydrates. Tuberculous guinea-pigs were used for the production of antisera and for the differentiation of the antigenic properties in vivo. Detailed data on the chemical nature of the various antigens are given. They all contain carbohydrates without apparent connection with the antigenic properties. It seems likely that in the lipoidal substances, protein fractions are responsible for the antibody production. Comparing different protein fractions and their action on guinea-pigs made allergic by various methods, it is evident that different tuberculin preparations have not only quantitative but qualitative differences as well. Only protein substances have a tuberculin effect and all these substances have, with few exceptions, antigenic properties in vitro. The tuberculin effect is probably one of several manifestations of the specific properties of antigens.

MAX PINNER

ANAPHYLAXIS (RABBIT) L H BALLY J Immunol **17** 191, 207 and 223, 1929

The reactions of the sensitized rabbit on reinjection were studied under ether anesthesia.

THE ANTIGENIC PROPERTIES OF BACTERIOPHAGE E W SCHULTZ, J S
QUIGLEY and L T BULLOCK, J Immunol **17** 245, 1929

The results indicate that the bacteriophage-antibacteriophage reactions closely parallel the toxin-antitoxin reaction, but this does not indicate of necessity that the bacteriophage is a toxin or a ferment.

THE RETICULO-ENDOTHELIAL SYSTEM AND ANTI-BODY PRODUCTION EDWARD F
ROBERTS, J Immunol **17** 273, 1929

A reticulo-endothelial blockade accelerates by approximately 50 per cent the rate of disappearance of precipitinogen from the circulating blood of the rabbit. Quantitative determinations indicate that the accelerated rate of antigen disappearance is a gradual procedure. Evidence is adduced to show that this effect of a reticulo-endothelial blockade on antigen disposal is attributable to an increase in endothelial permeability rather than to a serum factor.

AUTHOR'S SUMMARY

STUDIES IN HYPERSENSITIVENESS ROBERT A COOKE and W C SPAIN, J
Immunol **17** 295, 1929

Our studies have not disclosed any fundamental differences between the skin-sensitizing antibodies that are present in the three types of sera studied. Such antibodies seem to be quantitatively greater, more active and more regularly found in man than in the animal, for in man both naturally and artificially sensitized, the clinical evidences of the reaction are largely in the skin and mucous membrane.

Fundamental differences, however, may yet be shown, but as far as facts now go there is no warrant for assuming any difference in the biologic reaction of natural and artificial sensitization in the sense that the reaction is mediated by an antibody mechanism. The varying manifestations would seem to be explained by the fact that the reaction depends on the kind or the relative proportion of the sensitizing antibodies as well as on their number and their activity. But in spite of this recognition of a basic similarity, there is still, clinically, a vast and important difference between the naturally and the artificially sensitive man. This difference lies not in the nature of the reaction but in the constitutional make-up of the man. The naturally sensitive man constitutes a limited group with an inborn capacity for developing a particular, predetermined, and self-perpetuating sensitization. This stamps him as different from his fellow-man, and makes a distinction which is warranted by its clinical value and which for the present should be maintained.

AUTHOR'S SUMMARY

A NOTE ON THE ANTIGENICITY OF CRYSTALLINE EGG ALBUMIN R C LANCEFIELD and J H QUASTEL, *J Path & Bact* **32** 771, 1929

Dried, salt-free crystalline egg albumin, recrystallized six times, has been prepared, the analytic results and optical rotation agreeing closely with the figures of Hopkins. Evidence is brought forward to show that no alteration in the properties of the albumin had occurred up to the time of injection into rabbits for the purpose of immunization. Adequate antibody production was observed in all instances after a short course of immunization.

AUTHOR'S SUMMARY

COMPARATIVE IMMUNIZING EXPERIMENTS ON GUINEA-PIGS WITH BCG, SCHRODER'S VACCINE, AND KILLED TUBERCLE BACILLI O KIRCHNER and H F NEWTON, *Beitr z Klin d Tuberk* **72** 97, 1929

Three series of guinea-pigs of thirty animals each were immunized with BCG, Schroder's Vaccine and killed tubercle bacilli, respectively. They, and a fourth series of thirty unprepared guinea-pigs, were infected seven weeks after immunization, intracutaneously, with 0.003 and 0.0003 mg, respectively. The controls died (or were killed) from two to three months after infection. The BCG immunized animals developed the lesions in the regional glands considerably later than the controls, but they all showed extensive tuberculosis at autopsy. The other two methods did not seem to have increased the specific resistance.

MAX PINNER

THE FATE OF THE TIMOTHY BACILLUS IN THE ANIMAL ORGANISM W JELIN, *Centralbl f Bakteriol (Abt 1)* **111** 391, 1929, **112** 67, 1929

Jelin made a histologic study of the organs of twenty-five guinea-pigs, infected with the timothy bacillus. In the lungs, many small nodules developed within from 6 to 14 days, which consisted of two zones, viz, a central zone in which necrobiosis and degeneration of the nuclei of the polymorphonuclear leukocytes was prominent and a peripheral zone composed mainly of epithelioid cells and polyblasts. Later, the surrounding tissue is infiltrated by polyblasts, epithelioid cells and fibroblasts. No caseation occurs in the nodules, however. Giant cells are occasionally seen in the nodules. The alveolar walls become thickened, as do those of the blood vessels. Around the bronchi and blood vessels, a rich development of young connective tissue is observed. In the liver, small nodules form around the blood vessels. A deposition of glycogen and fat is observed in the cells of the nodule, but this and the nodules disappear in a few months. A slowly developing glomerulitis and at times some interstitial nephritis are observed in the kidneys. In the spleen and lymph nodes a nonspecific inflammation arises, accompanied by a hyperplasia with, later, a thickening of the capsule.

When dead timothy bacilli are injected, the same processes are observed as described, but they regress more quickly.

PAUL R CANNON

THE PHAGOCYtic POWER OF LEUKOCYTES AS INFLUENCED BY BACTERIOPHAGE
J C GERARDS, *Centralbl f Bakteriol (Abt 1)* **111** 493, 1929

A virulent strain of Shiga dysentery bacillus and a staphylococcus were used and bacteriophage prepared for each, which were specific. A bacteriophage vaccine was prepared and injected intravenously into experimental animals. The effects of bacteriophage on phagocytosis were tested, and the results indicated that in vitro and in vivo the bacteriophage has a specific opsonizing effect.

PAUL R. CANNON

EXPERIMENTAL STUDIES ON TISSUE SENSITIVITY OF JOINTS H. KLINGE, *Verhandl d deutsch path Gesellsch* **24** 13, 1929

Guinea-pigs were sensitized to a protein by intracutaneous injection, and after varying periods this protein was injected into the knee joints. In some animals the ischiadic muscles were cut through so as to produce impaired function and ankylosis of the joint. In typical cases a severe arthritis and peri-arthritis resulted. There was papillary hypertrophy of the synovial membrane, and the joint cavity was enlarged by a cell containing exudate. The character of the exudate was variable. After repeated large doses, there was a phlegmonous or necrotic reaction and a purulent exudate. After smaller doses, there was a mixed leukocyte, monocyte and histiocyte reaction. After many months, there were no leukocytes, although foci of necrosis and subendothelial hyaline degeneration were noted. Bodies similar to Aschoff bodies were encountered in the interstitial tissue of the joint and about the joint vessels. The muscles in the joint region had undergone waxy degeneration. There were glassy nodules on the mitral and aortic valve leaflets and basophilic large celled nodules in the cardiac muscles.

GEORGE RUKSTINAT

PATHOLOGIC ANATOMY OF TUBERCULOSIS OF LUNG IN MONKEYS W. H. STEFKO, *Virchows Arch f path Anat* **272** 573, 1929

In *Macacus rhesus*, *sinicus* and *cynomolgus*, the inflammation in nodules of the lungs is of the anergic type, the connective tissue does not react, and epithelioid cells and giant cells are absent. There is little perifocal reaction, no well defined zones are found. This represents an "alterative" inflammation, a type seldom found in the human being. In cynocephalidae (*Mandrillus pavian*), some epithelioid cells and fibroblasts appear as first signs of allergic inflammation. In one tubercle in the pharynx, epithelioid cells and one giant cell were found. The difference in the mesenchymal reaction between *Macacus*, *Cynocephalus* and man may be explained by a more primitive character of mesenchyme in man. Man has many primitive characters that monkeys have lost.

ALFRED PLAUT

PHARMACOLOGY OF RETICULO-ENDOTHELIAL SYSTEM MARCEL HAENDEL and JUAN MALET, *Virchows Arch f path Anat* **273** 127, 1929

The storage of india ink was decreased by a previous injection of epinephrine. It was increased by hypophysin, insulin, thyroïdin and ovarin. Glycerin decreased the storage power, therefore, glycerin extracts of glands cannot be used.

ALFRED PLAUT

THE PROPERTIES OF DIPHTHERIA TOXIN-ANTITOXIN MIXTURES H. SCHMIDT and W. SCHOLZ, *Ztschr f Immunitätsforsch u exper Therap* **58** 98, 1928

An otherwise fatal diphtheria toxin-antitoxin mixture appears under favorable experimental conditions as nontoxic for guinea-pigs, if the animals are sensitized with the normal serum homologous to the antitoxin. If the guinea-pigs are sensitized to another protein, then no difference is noticed between sensitized and

untreated animals after the injection of the toxin-antitoxin. If the sensitized animals are desensitized through a reinjection of homologous serum, then they are relatively insusceptible to diphtheria toxin. The authors present the supposition that a resulting protein-antiprotein reaction takes place in the body and that certain toxin-susceptible cell groups important for the formation of antitoxin are blockaded. It is suggested that these facts be considered in the practice of active immunization against diphtheria.

ROY C. AVERY

PRODUCTION OF THROMBOCYTOBARINE. M. N. LEBEDEVA, *Ztschr f Immunitätsforsch u exper Therap* 58 255, 1928

By immunization with bacteria it appears that only spirilla and vibrio possess the capacity to form thrombocytobarine. Bacilli and cocci cannot be employed as thrombocytobarinogen. These thrombocytobarines are specific for the bacteria. After impairment to the living functions the bacteria, like the spirochetes and trypanosomes, lose the capacity to adhere to the blood platelets in the presence of thrombocytobarine.

ROY C. AVERY

ISOLATION OF SERUM PRECIPITINS. GONZO SUKOUCHI, *Arch a d med Universitat zu Okayama* 1 1, 1928

Precipitin antiserum against beef serum is treated with some dried, powdered antigen. The precipitate formed is removed by centrifugalization, washed with physiologic solution of sodium chloride, suspended in distilled water or physiologic solution of sodium chloride and then tested with beef serum. The highest titer is obtained when the precipitate is shaken with water for from one-four to one-half hour at from 53 to 55 C. from which the author concludes that antigen-antibody precipitate is decomposed most completely under those conditions. The complement-fixation antibody is found with isolated precipitin, in equal amounts, from which the conclusion is drawn that precipitin and amboceptor are identical.

ARTHUR G. COLE

Tumors

SUPERFICIAL EPITHELIOMATOSIS. HAMILTON MONTGOMERY, *Arch Dermat & Syph* 20 339, 1929

According to Montgomery, superficial epitheliomatosis is a primary epithelioma of the skin clinically distinct. The characteristic lesion is single or multiple. It is a superficial, erythematous, scaling plaque with a rolled, threadlike, elevated border. Superficial epitheliomatosis is a frank basal cell, basal squamous cell or squamous cell epithelioma occurring usually on the trunk and as a rule having a benign course, but which may become malignant, metastasize and cause death. Data are given on a series of eighteen patients with this disease.

FRANK M. COCHEMS

EXPERIMENTAL SARCOMA OF BONE. CHARLES L. CONNOR, *Arch Surg* 19 794, 1929

The author obtained a tumor of an endothelial structure which was found in a chicken by Dr. Murray, director of the Cancer Research Fund in London. The material was dried and suspensions of this were used in an attempt to reproduce the tumor in other chickens. It was found that this suspension gave rise to a rapidly growing tumor when it was injected into the thigh muscles in chickens. In this tumor it was not possible to determine its cellular origin, but it did, in general, have an endothelial structure and resembled in some instances the structure of Hodgkin's lymphosarcoma. When the suspension was injected into the bone-marrow, the tumor growth could be recognized on the fourth day by microscopic examination. Here, too, it was difficult to determine from which cells the

tumor was growing, although it did appear to rise from the undifferentiated cells of the bone-marrow. As the tumor progressed it grew up and down the medullary cavity, finally penetrating the bone to grow between it and the periosteum. The first gross evidence of tumor appeared on the fourteenth day. However, two of the chickens died before this happened, and they presented metastases in the liver and spleen. A parallel experiment was done using the Rous fibrosarcoma, and it was found that this tumor presented on the sixteenth day as a fusiform tumor similar to that formed by the endothelioma. The endothelial tumor was not an exact reproduction of that described by Ewing, since it possessed also some characteristics of an osteogenic sarcoma. It filled the bone-marrow cavity generally and seemed to possess an osteolytic power, but later, as it penetrated the bone and grew beneath the periosteum, it apparently stimulated bone formation. Bone formation occurred in the Rous tumor as well. In both instances, this happened when the cells were confined between the periosteum and the cortex of the bone. The author feels that the bone formation in this particular location indicates that endothelial cells and fibroblasts, when placed in a suitable physicochemical medium, may differentiate into osteoblasts.

N ENZLR

OLIGODENDROGLIOMAS OF THE BRAIN PIRCHAI BAILLY and PAUL C. BUCY,
J Path & Bact **32** 735, 1929

Proof has been obtained, by specific impregnations, of the existence of brain tumors composed essentially of oligodendroglia. These tumors are predominantly situated in the cerebral hemispheres of adults. They almost invariably contain sufficient deposits of the salts of calcium or iron to be visible in x-ray films. Oligodendrogliomas are slowly growing gliomas with a relatively good prognosis. The records of four such tumors are given in detail as well as data concerning nine other proved and four presumptive cases.

AUTHORS' SUMMARY

ETIOLOGY AND PATHOLOGY OF PRIMARY LUNG TUMORS NORAH H. SCHUSTER,
J Path & Bact **32** 799, 1929

Primary pulmonary tumors are becoming more frequent. There is no known etiologic cause. Sarcoma may occur. Primary thymic tumors may invade the lung by direct spread. The vast majority of tumors are epithelial in origin. The persistent presence of columnar cells and mucin in the various types suggest an origin from the bronchial lining or mucous glands. It is impossible to distinguish histologically between tumors that arise from bronchial epithelium and those from the glands and their ducts. The small cell tumors are epithelial in nature and probably arise from bronchial structures. The existence of alveolar carcinoma is not proved.

AUTHORS' SUMMARY

MALIGNANT NEUROBLASTOMA OF THE SYMPATHETIC E. BULBRING, Virchows Arch
f path Anat **268** 300, 1928

A case of a tumor of the right suprarenal, the size of a child's head, with generalized metastases is described. It concerns a ganglioneuroblastoma connected with the medulla with remnants of the cortical tissue present. Numerous rosettes were found.

K. Hosoi

THE PRODUCTION OF TUMOR BY NAPHTHA PRODUCTS G. LEITMANN, Virchows
Arch f path Anat **268** 566, 1928

The author reports experiments on ten rabbits the ears of which were treated with a syrupy solution of toluene in petroleum. The changes were recorded six days, 20 days, two months, two and a half months, six months and eight months after the first application. The early changes were hyperemia, heat, swelling and loss of hair. In three animals, after six months papilloma and a cutaneous horn

developed The stimulus or "x" substance in the toluene was regarded as having produced an epithelial proliferation of typical blastomatous nature In all animals, cirrhosis of the liver was also found

V C JACOBSEN

HISTOLOGIC DIAGNOSIS OF CERVICAL CARCINOMA W SCHILLER, Zentralbl f Gynak 52 1562, 1928

Schiller described certain changes in the appearance and structure of the cervical squamous epithelium which he considers carcinomatous in nature and which he compares with Bowen's dermatosis The transition between normal epithelium and pathologic epithelium is always sharp As the diagnosis of carcinoma does not rest with definite morphologic changes nor on a histochemical test, he recommends staining the sections for glycogen with Best's carmine stain The normal epithelium will show glycogen granules, while the pathologic epithelium will not contain any granules or only a few

W C HUEPER

TUMORS OF THE OMENTUM E M FUSS, Zentralbl f Gynak 52 1782, 1928

Two cases of omental tumor are described One was a primary sarcomatous endothelioma and the other an isolated metastasis of a papillary carcinoma of the ovary Other metastasis was not present in either case

W C HUEPER

Medicolegal Pathology

INFLUENCE OF THE CADAVERIC MICROFAUNA ON DECOMPOSITION OF THE HUMAN BODY C F PORTA, Arch di antrop crim 49 3, 1929

This is a detailed study dealing with the classification and characteristics of various necrophagous species and their mode of destruction of dead human bodies, either exposed to air or interred, for the purpose of determining the time of death The author discusses the practical value of the classification of the cadaveric fauna first attempted by Megnin in 1884, he reviews the additional entomologic investigations on this subject published since and classifies the known necrophagous parasites Applying the postulates of Megnin, the study of the parasites present in the decaying body and the chronologic succession of the various insects allows one to determine the time of death, but only approximately Of course, the meteorologic conditions also have an important influence on the disintegration of the cadaver The necrophagous fauna varies according to the soil and climate For instance, in stony soil, *Carabidae*, *Tenebrionidae* and *Staphylinidae* prevail, in cultivated earth *Thanatophilus*, *Silpha* and *Acanth* are frequently present, in forested or woodlands *Diptera* (of the genus *Lucilia*, *Muscina*, *Sarcophaga*, etc) are common, while in swampy countries and along running waters *Necrodes* and *Cecyon* are often found The investigations have disclosed that during the various stages of disintegration, certain characteristic insects are found 1 During the chromatic stage *Diptera* (*Lucilia*, *Musca*, *Muscina*) and *Hymenoptera* (*Vespa*) appear 2 In the second or emphysematous stage, *Coleoptera* (*Staphylinidae*) and *Diptera* (*Sarcophaga*, *Calliphora*) are observed 3 During the first part of the colliquative stage (initial colliquation) *Coleoptera* (*Hister*, *Necrophorus*, *Silpha*, *Saprinus*, *Thanatophilus*) are seen, while the second period of this same stage (terminal colliquation) is characterized by the appearance of *Coleoptera* (*Dermeestes*), *Diptera* (*Phora*, *Cynomyia*, *Lonchoea*, *Anthomyia*, *Pyophilus*, *Fannia*, *Scathopse*, *Ophyia*) and finally of *Lepidoptera* (*Aglossa*) 4 During the preskeletal stage *Acanth* and several types of *Diptera* (*Thysanophora*, *Phora*) appear 5 In the last period or stage of skeletization we meet *Coleoptera* of the genus *Anthrenus*, *Attagenus*, *Ptinus*, *Tenebrio*, *Tenebriones*, etc, a few *Lepidoptera* (*Tinea*, *Tineola*), and finally *Hymenoptera* (*Lasius*, *Solenopsis*) and *Thysanura* Larvae may be encountered in any of the mentioned periods, which, of course, are not sharply defined, one may find, on one and the same cadaver, larvae and insects characteristic of various stages of decomposition Only a predominance

of a certain species should be taken into consideration. The disintegrating action of the insects on a dead body exposed to open air, as to the sun in the summer months, in places in which the necrophagous fauna is richly represented, is about fourteen times as rapid as on cadavers found in cellars or rooms, or in enclosed or covered spaces, where the microfauna does not enjoy the optimal requirements for development.

E. L. MILOSLAVICH

Technical

THE TECHNIQUE AND RESULTS OF A COMPLEMENT FIXATION TEST FOR THE DIAGNOSIS OF INFECTIONS WITH *ENDAMEBA HISTOLYTICA* CHARLES F. CRAIG, *Am J Trop Med* 9 277, 1929

It is believed that the results of the complement fixation test for infection with *Endameba histolytica* demonstrate that substances occur in the blood serum of persons infected with this parasite, probably produced as a result of the reaction of the cells to the infection, which are specific in nature and which are capable of fixing complement when the serum is mixed with an alcoholic extract of cultures of this organism. It is not believed that this substance (or substances) is a true immune antibody. While the exact nature of the antibody is at present unknown, it certainly belongs to that group which is extracted with alcohol. Clinically, and as checked by the microscopic and cultural examination of the feces, the test would appear to possess a high degree of specificity, and its use in hospital practice has revealed amebic infections that would otherwise have remained unrecognized. The technic of this complement-fixation test is intricate and should be attempted only by a trained serologist.

JOHN PHAIR

HYDROLYZED SERUM AGAR FOR THE ISOLATION OF *CORYNEBACTERIUM DIPHTHERIAE* LUTHER THOMPSON, *J Infect Dis* 45 163, 1929

A serum agar has been prepared by treating Loeffler's blood serum, dehydrated, with sodium hydroxide and incorporating the noncoagulable product in agar. The medium promotes the growth of diphtheria organisms, and inhibits certain other organisms found in the throat. It is easily available, easily prepared, can be safely sterilized in the autoclave and offers the convenience of an agar medium for the plating and isolation of pure cultures of *Corynebacterium diphtheriae*.

AUTHOR'S SUMMARY

A SIMPLE METHOD OF MAKING CULTURES OF THE RECTUM E. F. TRAUT and R. D. HERROLD, *J Infect Dis* 45 172, 1929

Massage of the rectum with sterile petrolatum-coated finger cot or glove, followed by inoculation of its tip on to blood agar plates, gave cultures of streptococci and other bacteria in larger numbers as compared with the colon bacilli than could be secured by making cultures from the feces. The persistence of similar bacteria on repeated culture would indicate that the organisms found are not accidental saprophytes. A comparison of the fermentations by the streptococci isolated on successive culture is further evidence of the reliability of the results. The method offers an easy means of studying the relations of pathogenic bacteria of the rectum to disturbances of the intestinal tract itself, and also to arthritis and other systemic diseases.

AUTHORS' SUMMARY

STUDIES ON ANTIGEN FOR THE KAHN TEST. PROPERTIES OF SENSITIZED ANTIGEN G. LUBIN, R. L. KAHN and M. B. KURTZ, *J Infect Dis* 45 196, 1929

Sensitized antigens yield more sensitive reactions than standard antigen with syphilitic serum and cerebrospinal fluid. The sensitiveness is at a maximum

when the antigen contains an optimum proportion of sensitizing reagent and the total concentration of extractives is suitably adjusted. A further increase in the proportion of sensitizing reagent results in a decrease in sensitiveness. Sensitized antigens require a larger proportion of salt solution than standard antigen to give dispersable suspensions. Within certain limits the titer increases with the amount of sensitizing reagent present, reaching a maximum value which remains practically independent of further addition of reagent. Sensitized antigens are more susceptible than standard antigen to changes in the sodium chloride concentration and the p_H of the salt solution with which the alcoholic extract is mixed, and are more rapidly affected by exposure of the extract to sunlight.

AUTHORS' SUMMARY

A PRECIPITATION TEST FOR SYPHILIS. EMIL WEISS, J. Infect. Dis. **45** 225, 1929

The efficiency of the proposed test is based mainly on the concentration of reagents. The new method has the following advantages over the Kahn test. The dilution of the antigen is simpler and requires less time. The titration of the antigen is more accurate, being based on the reaction with serums or spinal fluids, respectively. The preparation of the antigen-serum mixture is simpler. The spinal fluid is added directly to the antigen dilution, thus avoiding the complicated procedure of concentrating globulins. The precipitation is produced by the combined effect of lipoids and sodium sulphate, and is very definite. The reading is facilitated by the higher dilution of the antigen-serum mixture at the conclusion of the test. The reading of results is more accurate and better defined. The entire routine test and the quantitative procedure are greatly simplified. The test gives a higher percentage of results agreeing with the results of the Wassermann test.

AUTHOR'S SUMMARY

CATHETERIZATION OF THE RIGHT SIDE OF THE HEART. W. FORSSMANN, Klin. Wchnschr. **8** 2085, 1929

The author describes the insertion into his own median basilic vein of 65 cm. of a ureteral catheter, and demonstrated by roentgen examination that the tip of the catheter extended into the right auricle of the heart. Dextrose solution containing other medicaments was given intracardially in this way to a moribund patient with apparently some beneficial effect. This method may be useful in studying metabolism and in investigating the functions of the heart.

EDWIN F. HIRSCH

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Anniversary Meeting, Jan 23, 1930

HARRISON S. MARTLAND, *President, in the Chair*

BILE ACIDS, BILE PIGMENT AND CHOLESTEROL OF A, B AND C FRACTIONS OF BILE J. CARLIND BROWNE, I. KATAYAMA and J. A. KILLIAN

Bile was aspirated from the duodenum before and after the administration of magnesium sulphate. The siphonage of bile obtained after the administration of magnesium sulphate was divided into A, B and C fractions according to the technic of Lyons. Observations were made on thirty-five satisfactorily fractionated specimens from ten patients with chronic cholecystitis whose icterus indexes varied from 58 to 94.

Total solids, magnesium, bile pigment, bile acids and cholesterol were determined in the fractions of bile. The bile acid concentration of B bile was from two to ten times greater than that of A and C. Bile pigment in B bile was from four to twenty-five times greater than that of A and C bile. The cholesterol of A and C was uniformly less than that of B bile. A comparison of the magnesium of the A, B and C fractions of bile with the magnesium content of bile before the administration of magnesium sulphate has made it possible to compute the probable dilution of the bile with magnesium sulphate solution. These calculations indicated that the magnesium sulphate solution formed from 20 to 53 per cent of the A bile, from 16 to 23 per cent of the C bile and from 10 to 20 per cent of the B bile. It appeared significant that the total solids of B bile were definitely greater than the total solids of A or C bile, although the A and C fractions contained more magnesium sulphate. When the analyses of the bile fractions were corrected for dilution with magnesium sulphate solution, it was found that the bile pigment of B bile was twelve times greater than that of A, and three and four-tenths times greater than that of C, the bile acids of B bile were eight and one-half times their concentration in A, and three and seven-tenths times their concentration in C.

Comparisons have been made of the concentrations of bile pigment, bile acid and cholesterol of the bile fractions with their concentrations in the blood of the subjects drawn at the time of the biliary drainage. In these comparisons the concentrations of the three components of the bile have been corrected for dilution with magnesium sulphate. The cholesterol content of the A and C fractions was much less than that of blood, but the B fraction had a cholesterol content about twice that of blood. The bile acid and bile pigment content of the three fractions was definitely greater than that of the blood serum.

CHLORIDES OF GASTRIC CONTENTS IN HYPOCHLORHYDRIA AND HYPERCHLORHYDRIA KATHERINE EYERLY and JOHN A. KILLIAN

Free hydrochloric acid, total acidity, inorganic chlorides and total chlorides have been determined in specimens of gastric contents aspirated at intervals of fifteen minutes for two hours from patients who had received a salt-free meal, as described by Rehfuess. Results have been expressed in terms of milli-equivalents of chlorine per cubic centimeter. Graphs were presented to illustrate the principles of interpretation of the results.

Synchronous graphs for total chlorides and inorganic chlorides with curves for free hydrochloric and total acidity furnish data on the mechanisms producing achlorhydria or hypochlorhydria, i. e., the neutralization of gastric acidity by the ingestion of food, regurgitation of duodenal contents or a deficiency in secretion of hydrochloric acid. In the study of the production of hyperchlorhydria, these graphs may be utilized as indicators of hypersecretion, hyperperistalsis or a lack of neutralization.

A CASE OF FULMINANT INFECTION WITH THE PFEIFFER BACILLUS ADELE E SHEPLAR, LAWRENCE SOPHIAN and WARD J MAC NEAL

This case is presented in abstract because of several unusual features. In the first place, the clinical course was unusually rapid and led quickly to a fatal issue. In the second place, it was possible to demonstrate that the inciting organism was the Pfeiffer bacillus, and the organism was demonstrated in the respiratory tract, the lungs and the brain.

The patient was a boy, aged $3\frac{1}{2}$ years, who had been apparently well up to about 2 p. m. on December 16. At that time he began to complain of feeling ill and was put in bed. The temperature reached 106.5 F. that evening. During the night, severe convulsions took place, and the patient died in a convulsion about 9 a. m. the following day. Autopsy was performed at 3 p. m. The positive observations were a hemorrhagic injection of the mucosa of the trachea and bronchi, a moderate hemorrhagic injection in scattered foci in the lungs in all the lobes, and, in the meninges, a definite fibrinopurulent exudation over the cortex and base of the brain, extending down into the spinal meninges as well. The ears were normal. A smear of the meningeal exudate made at autopsy revealed a large number of polymorphonuclear leukocytes, and in and about these were seen abundant bacteria which ranged from small rod-shaped to fairly rounded coccoid forms. These were all gram-negative, staining very faintly with the counter stain. The organisms were mainly inside the leukocytes. A smear made from the injected foci in the lung showed a moderate number of pus cells, some of which were seen to contain gram-negative rods. There were also occasional groups of bacteria outside the cells. A culture of the spinal fluid was made on chocolate blood agar which within twenty-four hours showed very faint delicate colonies that did not grow on plain agar but that grew more luxuriantly in subculture on chocolate blood agar. These colonies consisted of pleomorphic gram-negative bacilli. Intra-peritoneal injection of these cultures into mice did not kill the animals.

Microscopic examination of the meninges showed an extensive, purulent exudate filling the subarachnoid space, and some of the polymorphonuclear leukocytes invaded the superficial portion of the cortex of the brain, which was extremely edematous. Sections of the primary bronchi showed extreme engorgement of the capillaries of the mucosa and submucosa. Rather numerous mononuclear and polymorphonuclear leukocytes were noted between the epithelial cells and in some places on the surface of the mucosa in the lumen of the bronchioles. About the bronchioles the exudate was found to extend into the alveolar walls, separating the distended alveoli from one another by masses made up largely of red blood cells together with some mononuclear and polymorphonuclear leukocytes. The exudation was therefore within the alveolar walls rather than within the air spaces. The sections were stained with a modification of the eosin and methylene blue (methylthionine chloride, U. S. P.) stain in which, instead of methylene blue, azure B was used. This gave a powerful stain, and the bacteria could be seen stained dark blue or bluish purple in and about the leukocytes, in the bronchi, in the alveolar walls and in the meningeal exudate.

From this demonstration of the identity of this bacillus and its presence in the tissues in a case in which it appears to be the primary invader, we apparently have a new bit of evidence in regard to the potentialities of the Pfeiffer bacillus in producing disease under appropriate conditions.

DISCUSSION

WARD J MAC NEAL I regard this case as of considerable importance because of the prolonged controversy that has existed since 1918 in regard to the etiology of epidemic influenza. We are not in a position to say that this is a case of epidemic influenza. We are in a position to say that it is an instance of a fulminating infection with the Pfeiffer bacillus. During the postmortem examination, before the cranium had been opened, the appearance of the bronchi and of the trachea was such as to cause the prosecutor to remark, "This is the sort of influenza we saw in France in 1918." The invasion of the meninges by the same organism, which has been demonstrated in the walls of the pulmonary alveoli, indicates that this organism was the important factor in the death of this child, who was, at 3 o'clock on the previous afternoon, actually playing outdoors. We can still afford to pay attention to some of the things we knew about influenza previous to 1918.

SOME OBSERVATIONS OF THE BACILLUS OF DUCREY ADELE E SHEPLAR and
WARD J MAC NEAL

The discovery of Ducrey, who showed the presence of a small hemoglobinophilic, gram-negative, thread-forming, cylindric microbe in soft venereal sore, has been widely confirmed, and there is no longer any serious question that this organism causes a definite type of chancroid. However, the bacteriologic studies of soft chancre in various parts of the world have in some instances failed to disclose bacteria of this type, and on that account the specific relation of the bacillus of Ducrey to the common forms of chancroid and to chancroidal bubo have been questioned and in many clinics the Ducrey bacillus has been frankly disregarded.

The modern bacteriologic technic for chancroid has been developed by Teague and Deibert in America, Saelhof in England and especially by Paul Durand in Tunis.

For the last two years the presenters have employed a simple technic, essentially that of Durand, in making cultures from soft venereal ulcers. From 15 to 20 cc of blood is taken from the elbow vein of the patient and most of this is distributed to miniature tubes in amounts of 1.5 cc each, a portion being reserved for the usual serologic tests for syphilis. The tubes are slanted and left undisturbed until firm clot has formed. The sore is then carefully cleansed with cotton moistened with salt solution, a somewhat painful ordeal for the patient. Minute portions of exudate and of granulation tissue are removed from the base of the ulcer, preferably by means of sterile glass capillaries with cutting edges. These bits are seeded in the serum on the surface of the clotted blood. At least one such specimen of fresh material is smeared and stained for direct microscopic study. The culture tubes are placed at from 35 to 37 C in the slanted position. After twenty-four hours, microscopic examination of the exuded serum on the clot usually reveals the bacteria, but the transfer of a large drop of this serum, by means of a sterile glass pipet, to the surface of a slant of mixed blood agar results almost invariably in the development of typical colonies of the Ducrey bacillus and usually without admixture of contaminating bacteria on the blood agar slant. After isolation the cultures remain viable in stoppered tubes of human blood agar at 35 C and require transfer at intervals of one month.

Autogenous vaccines prepared from such cultures have given excellent clinical results in a small series of cases.

DISCUSSION

JAMES EWING What is the histology of these lesions?

WARD J MAC NEAL We have not had enough material to make histologic examinations. The piece we obtain is only 0.5 mm in diameter.

HARRISON S MARTLAND In your studies of the Ducrey bacillus in chancroids, can you identify the organisms in the dark field examination, or even suspect the infection?

WARD J MAC NEAL No, I do not think so, they are seen there as little dancing particles

THE INFLUENCE OF ENVIRONMENTAL FACTORS ON THE BEHAVIOR OF
ESCHERICHIA COLI AND ITS SPECIFIC BACTERIOPHAGE IN URINE FRANCES
C FRISBEE and WARD J MAC NEAL

The colon bacillus grows well in human urine in a p_H range from 5.8 to 7.2 and most abundantly in the range from 6.5 to 6.8. The lytic action of bacteriophage added to such cultures in urine was most effective in the p_H range from 5.6 to 6.3, with a sharp inhibition of the lytic action at p_H 5.3 and a more gradual diminution of the lytic action toward the alkaline side beyond p_H 6.3. Exclusion of air appeared to be without significant influence.

Formaldehyde in a concentration of 1 per cent prevented visible growth of the colon bacillus in urine. In a concentration of 0.1 per cent, the bacillus grew and the lytic action of the phage was inhibited. Slight inhibition of the phage was evident in cultures containing one part formaldehyde per hundred thousand, but was not clearly discerned in a formaldehyde strength of 1 per million in urine.

Acridine, 1:10,000, inhibited the growth of the colon bacillus in urine. At 1:10,000 it allowed growth of the bacillus and inhibited the phage, especially in a p_H of 6.5 or less. Even at 1:1,000,000 a slight inhibition of the bacteriophage could still be recognized.

It would therefore appear that the treatment for infections of the urinary tract due to the colon bacillus by use of bacteriophage may be favored by maintaining a slight acidity of the urine. It is also evident that the formaldehyde and acridine are unfavorable to the action of the bacteriophage.

DISCUSSION

WARD J MAC NEAL This work makes no pretense of having any bearing on fundamental scientific questions. It is an attempt to study applied science, applied to a particular medium and in relationship to a particular type of human disease. However, when one starts out to investigate such a practical problem one sometimes finds evidence of general scientific value. It is evident that the two antiseptics tested exert a more powerful effect on the lytic agent than they do on the bacterial culture which is to be dissolved. Whether one can draw any definite conclusions as to the nature of the bacteriophage from such an observation I am unable to say, but it is true that we know of many enzymes which are capable of acting in the presence of an antiseptic, which is able to suppress entirely the cells producing such enzymes. Our observations would therefore tend to support the conception that the bacteriophage is a particulate living agent rather than an enzyme produced by the bacteria.

THE RELATION OF THE EPITHELIUM TO THE MUCOSA IN PACHYDERMIA
LARINGIS (WAX MODEL) LOUISE H MLEKER

The practical necessity of making a diagnosis from small bits of tissue rarely more than a few millimeters in diameter has stimulated this investigation. Sections from the larynx at various ages have been the basis of the study.

Vocal cords and their attachments have been dissected from persons aged 2 and 4 months and 2, 4, 11, 36 and 80 years, respectively, and coming to autopsy with no history of laryngitis. This material was cut in horizontal and vertical transverse and sagittal sections. The arrangement of the epithelium and mucous glands about the vocal process of the arytenoid and the elongation of the gland ducts with the ingrowing squamous epithelium seemed distinctive of this area, the area including the folding of mucosa adjacent to the vocal process. The notable points were the great activity of the squamous epithelium, with the rapid filling in of the wide ampulliform surface openings of the ducts with fusion into solid masses.

at all ages. Within the deeper gland ducts, papillary thickenings of the epithelium, as well as a tendency to metaplasia, were very common.

The next step was the application of these pictures to frankly pathologic hyperplasia to ascertain when a diagnosis of a malignant condition was justified. The accredited signs of malignancy were checked off one by one in a selected example of pachydermia laryngis that we had considered on the borderline between a benign and a malignant process. The tissue was both nodular and diffuse and had been removed from a man, aged 39 years. In this case greater activity of the epithelium was found than was seen in the normal mucosa. We also found larger and more numerous papillae. Ingrowing of the squamous epithelium in the ampullae of the gland ducts and increase in the number of layers were noticeable, but atypical forms of cells were scarce. We found metaplasia and fusion in these areas with but little epithelial activity. Deeper in the glandular ducts we found changes all the way from papillary tufts to metaplasia of a few cells to metaplasia *en masse*, also increase in layers and fusion to form deeply placed islands. The proliferative activity was less here than near the surface, and the metaplasia followed the usual mode of transition seen normally on the surface. The activity of the surface epithelium together with the large and wide papillae indicated the third step in the study.

A nodule, showing many irregular papillae and numerous mitotic figures in microscopic sections, was chosen for a wax model. Fifty sections cut 10 microns thick in series were magnified 100 times by the Edinger apparatus. The numerous mitotic figures were marked wherever they occurred in a section by placing an opaque bead for each in the wax replica. The sections averaged 30 mitotic figures each, totaling 1,600 for a sector measuring 2.5 mm in diameter and 0.5 mm in thickness. The uppermost section showed 40 mitotic figures. The presenter depended on this method to discover whether there were any isolated foci of proliferative activity. The completed model was photographed, and x-ray pictures were made. The mitotic figures were seen evenly distributed at all points and in all layers.

The presenter compared the pathologic epithelial hyperplasia seen in a case of pachydermia laryngis, a "borderline case" with specimens of practically normal mucous membrane from the vocal process and posterior commissure.

The microscopic slides and the wax model studied somewhat lessened the seriousness of the first diagnosis.

DISCUSSION

JAMES EWING. Dr. Meeker's method is most ingenious and offers a means of study of many features of beginning carcinoma. The results obtained in pachydermia laryngis must make one extremely cautious in pronouncing an opinion concerning the clinical course of laryngeal lesions.

PAUL KLEMPERER. I think that we should be extremely grateful to Dr. Meeker for her investigations, because they emphasize the importance of great caution in diagnosing small fragments of laryngeal tissue and of making the diagnosis of carcinoma, only when we have all the criteria of carcinoma present. We should apparently not stress the possibility of carcinoma in a case in which we find downgrowths of epithelium alone, even with a considerable number of mitotic figures. Such a study, therefore, is extremely valuable because it confirms the more vague experience that all who do practical pathology encounter, and is helpful in our practical work.

ALFRED PLAUT. I think that the demonstration has practical and theoretical importance, not only for the larynx, but for other parts of the body where biopsies are obtained. These pictures remind one of the more or less atypical changes in the epithelium of the uterine cervix when the diagnosis on small particles of tissue has to be made. If such pictures are found frequently in autopsy material in which there is no suspicion of existing or developing carcinoma, then we have to be more and more careful concerning the term "precancerous." I never use

the term. Many people use it, and the people who do so certainly would use it for the pictures which Dr Meeker has shown. In the uterine cervix we know that such pictures must not have anything to do with carcinoma. The larynx and the uterine cervix have one thing in common, i. e., that different kinds of epithelium are together in very small spaces, and at the same time are subjected to much mechanical irritation. There may be some other parts of the body where these conditions are true, so aside from the practical importance, which was stressed by Dr Klempner, I think that it gives us an idea of the usefulness, or nonusefulness, of the theoretical term precancerous lesions.

HARRISON S. MARTLAND. For some time I have been of the opinion that the occurrence of a few mitotic figures should not be considered absolute proof of malignancy. These figures often occur in tissues like the endometrium, which is constantly undergoing profound changes in structure. The popular tendency to grade tumors on the appearance of one or a few isolated cells is risky indeed and often misleading. This accounts for the great increase in the so-called precancerous lesions and the so-called malignant changes in simple, benign, gastric ulcers. For these reasons, I believe that Dr Meeker's painstaking studies are of considerable importance.

PAUL KLEMPNER. Dr Plaut's remark recalls to my mind a case of tuberculosis of the lungs in which I made routine sections of the larynx looking for tuberculosis. To my surprise I found the most remarkable proliferation of the epithelium, even with irregularity of the cells, but on macroscopic reexamination of the larynx I could not find any evidence of tumor. In cases of tuberculosis, one has to be particularly conservative.

A RECONSTRUCTION STUDY OF THE FOLLICLES AND FOLLICULAR ARTERIES OF THE HUMAN SPLEEN. WARD J. MAC NEAL and J. M. RAVID

From earlier studies it has been concluded that the splenic circulation is essentially open, in the sense that the elements of the blood pass from the arterial terminations into the intercellular spaces of the pulp and thence through the stomas of Mollier into the venous sinuses. It was further concluded that the functional unit of splenic structure, or the splenic lobule, may be recognized as consisting of a central follicle, a bordering marginal zone and the radiating pulp cords. In a perfused specimen of spleen, the lobule is outlined by the most widely distended venous sinuses at its periphery.

The present study is concerned with a small terminal branch of the splenic artery and the splenic follicles supplied by it. The spleen of a child perfused and fixed in the distended state was used for a series of stained sections cut at a thickness of 5 microns. These sections were then projected and drawn at a magnification of 20 diameters. The outline drawing of every tenth serial section was transferred to a wax plate 1 mm thick, and the cut wax plates were fitted together with suitable wire support to form a wax model.

The model shows the follicles in relation to their special arterial vessels in a region including the external capsule of the spleen and extending about 10 mm beneath it into the splenic substance. The follicles more deeply situated are irregularly spherical and possess a single terminal artery of considerable length which enters the follicle and divides to supply only the lobule pertaining to that follicle. The coarser arterial twigs running out into the pulp carry sheaths which appear to be prolongations of the follicular substance, indicating that the ellipsoid sheaths are possibly of the same nature as the lymphatic tissue of the follicle.

Near the surface of the spleen, however, the follicles tend to be more elongated and narrow and tend to stretch along one side of an arterial branch which may continue on beyond to supply a follicle situated nearer to the external capsule. The appearance suggests that these lobules near the capsule may be less mature than those deeply situated. They still present the appearance of compound lobules of irregular shape, the individual follicles being not yet completely surrounded by large venous sinuses so as to define the lobule completely.

DISCUSSION

PAUL KLEMPERER I would like to ask one question. It seems from the model, particularly of the areas distant from the capsule, that the lymphatic tissue around the arteries is accumulated in the form of follicles only. In the portion nearer the capsule the lymphatic follicles seem to be elongated, more cylindric. I wonder if this elongation does not indicate that there is also, between the follicles, a lymphatic sheath around the artery. I remember the article and pictures of Hellsten (*Ztschr f mikr-anat Forsche* 13:43, 1928). He states that in human spleens there is always a lymphatic sheath around the artery between those portions of the vessel which are surrounded by a distinct follicle. I think that it is different in rabbits. The lymphatic tissue is arranged in continuous cylindric sheaths with only insignificant follicles. I remember that the cat was the third mammalian examined and there, if I am correct, conditions are similar or identical with those in human spleens. I should like to ask whether Dr Mac Neal did not find any lymphatic tissue arranged in cylindric sheaths between the follicles, though in moderate amounts.

WARD J MAC NEAL I am not sure that I appreciate Dr Klemperer's question. It is, of course, true that lymphatic sheaths occur about the vessels between the follicles, but it is not quite clear to me what type of vessel is referred to in the question. The arterioles of the pulp cords are surrounded in part by lymphatic sheaths, and the ellipsoids of Schweigger-Seidel are possibly of a similar nature. Without reconstruction studies such vessels may possibly be mistaken for larger trunks. As far as lymphatic sheaths for the larger arteries, which I would designate as intralobular arteries, those that I have spoken of as stems of the cherry, they are surrounded by venous pulp and do not possess a sheath which contains lymphoid cells. They have an ordinary arterial wall with a little adventitial tissue. They enter into the follicle in an abrupt fashion.

The follicles that are distributed along the arterioles are not found near the external capsule of the spleen. The significance of this arrangement is not clear to me. It is a question whether these represent developing portions of the spleen, analogous to the developing cortex in the kidney of a young child, or whether they represent fully developed lobules of a peculiar form. There is also the possibility of other explanations. It will be necessary to study other spleens before we decide.

PAUL KLEMPERER Of course, I meant the arteries of first magnitude, and I wonder if the model which was shown is not the exception to the rule. I think that the paper by Hellsten would indicate it.

WARD J MAC NEAL Did he use perfused spleens? When you perfuse a spleen you need examine only a single section to find intralobular arteries without lymphatic sheaths.

HISTOLOGIC STUDY OF SACROCOCCYGEAL CHORDOMA LAWRENCE SOPHIAN and NICHOLAS M. ALTER

This report is added to the approximately seventy cases already in the literature because of the relative rarity of this type of tumor. There is, however, still considerable confusion in regard to the pathogenesis and histologic nature of this lesion (other cases with similar histologic pictures have been described as myxochondroma, spindle cell sarcoma, colloid carcinoma, etc). Therefore, an attempt has been made to apply a variety of stains with the object of making as complete a histologic analysis of the tissue as possible.

A man, aged 44 entered the New York Post-Graduate Hospital complaining of pain in the back of two years' duration. Shortly after the onset he noted a lump in the sacral region. At the time of admission this lump had reached the size of a football, and there were also difficulty in defecation, frequency of urination and some incontinence. There was no bleeding into the rectum. Destruction of the lower portion of the sacrum and coccyx was seen by roentgen examination. An attempt was made to remove the growth, but two hours later the patient

died suddenly with severe pain in the precordium. This change was considered clinically as pulmonary embolism.

The pathologic specimen consisted of a growth weighing 7 pounds (3.2 Kg), with an outside surface partly covered by skin, having an area 21 by 7 cm. The mass showed partial encapsulation with numerous lobular subdivisions, some of which were transparent and jelly-like, others were fibrous, and still others, cystic. There were also numerous hemorrhagic foci. There was a considerable amount of fibrous tissue, some of which was loose, other portions were extremely tough and tendinous. Toward one surface numerous fragments of bone, apparently portions of the sacrum, some of considerable size, were noticed. Numerous sections from various parts of the tumor were studied and stained for evidence of metabolic and degenerative products. A great variation of cell type in different parts of the tumor was noted. In some foci there were many vacuolated physaliphorous cells in a loose syncytial arrangement. Elsewhere the tissue was dense with bundles of collagen about rather small compressed cells. Here the resemblance to scirrhous carcinoma was marked. The presence of glycogen within the large vacuolated cells has been noted by other authors. In the case presented the material was not available for this examination. Within and between the cells could be found a material staining with mucicarmine and also with the toluidine blue method for mucin recently described by R. J. Lillie. No material staining with sudan III or scarlet red could be demonstrated. By picrofuchsin, phosphotungstic acid-hematoxylin and Mallory's aniline blue stain, the presence of fibroglia and collagen fibrils could be determined between the cells of the tumor. These fibrils did not appear in relation to supporting stroma connective tissue but seemed rather to arise from the tumor cells themselves. The appearance suggests that these cells are an embryonal variety of fibroblasts secreting a fluid substance which expands the cells and then breaks out between them. When in the intercellular spaces this fluid apparently jells and becomes a fibrillar material which appears to be identical with collagen in staining characteristics. While the identification of the substance is not complete, it appears from the present evidence that the cells called chordoma cells are probably really embryonal cells capable of manifold differentiation, which secrete a substance that may become converted into collagen.

DISCUSSION

BORIS KWARTIN I should consider the presence of mucin a sign of degenerative changes in the neoplasm rather than a primary property of the cells, because the chorda cells proper in the nucleus pulposus, as well as the physaliphorous cells in the chorda dorsalis of the embryo, are free from mucin.

LAWRENCE SOPHIAN I cannot answer Dr. Kwartin's question exactly, but at least it is suggestive that mucous connective tissue is embryonal, the connective tissue that is seen in embryos and in the umbilical cord normally, when a question of degeneration does not come into play, is of this type. The occurrence of mucoid degeneration in connective tissue is seen in a great many other regions, and I have found areas of degeneration in which the presence of mucinous material cannot be questioned, however, when we are dealing with a tumor of embryonal origin, we should not be surprised to see that an embryonal variety of intercellular substance is also present.

NICHOLAS M. ALTER I have been interested in embryonal tumors for a long time, particularly from the standpoint of the intercellular substance as well as the intracellular secretion, both of which are often identical with substances found during degenerative processes in pathologic conditions. They are evidently due to changed cell metabolism, for example, the amyloids. Chemical analysis and study by special stains will also reveal a great variety of this substance, although all these varieties are probably related to chondroitin sulphuric acid. About two years ago I had the opportunity to talk before the Society on lipoblastoma. In these embryonal fatty tumors I also found a variety of intercellular substance that is also present in many other tumors, which are called simply

myxoma In some types of malignant chordoma, atypical amyloid, mucoid, collagenous and other interstitial substances are present

I also had the opportunity to observe some cases of chordoma clinically for a considerable time They have a long-continued benign period, after which they take a rapidly growing malignant course These tumors probably occur more frequently, but they are often confused with other tumors, they are often called benign chondroma or chondrosarcoma, or sarcoma of the pelvis

HARRISON S MARTLAND The tumor in question looks more like a chordoma than a great many cases of that disease reported in the literature Consider the myxomas of the bladder, it is a question whether they are not just ordinary edematous fibroblastomas and have nothing to do with mucin—Wharton's jelly

NEOPLASM DERIVED FROM MUCUS-SECRETING CYLINDRIC CELLS OF THE LINING OF THE URINARY TRACT NICHOLAS M ALTER and JOSEPH F MCCARTHY

Mucus-secreting cylindric cells can give rise to unusual neoplasms along the urinary tract Two such cases furnish the material for the present study One was malignant, a so-called mucoid carcinoma of an exstrophic urinary bladder, the other was benign, a mucinous adenocystoma of the pelvis of a horseshoe kidney Both of these cases were from the service of Dr Joseph F McCarthy at the New York Post-Graduate Medical School and Hospital

CASE 1—I S, a white man, aged 51, had been under observation for eighteen years He was admitted to the Post-Graduate Hospital sixteen times in the interval from October, 1919, to Oct 3, 1928 Previous to admission he had had nine operations for attempted closure of the bladder These closures, however, reopened from time to time There were symptoms also of mild infection of the urinary tract In 1922, the patient began to have hematuria, the fistula of the bladder became everted and the edges were covered with fungoid growth The growth was partly excised, and the patient was treated with diathermy Pathologic examination of this tissue revealed a papillary adenocarcinoma In November, 1923, Dr McCarthy performed an operation for total cystectomy and left ureterostomy to the anterior abdominal wall On Dec 20, 1924, as no renal function but purulent discharge was noted from the right ureter, Dr McCarthy performed a left nephrectomy, without the removal of the corresponding ureter The patient's last admission was on Sept 18, 1928, at which time he complained of headache, general weakness and drowsiness At that time the chemical analysis of the blood showed urea nitrogen, 41.6, creatinine, 5.7 The patient died on October 3, with symptoms of uremic acidosis Autopsy was performed twelve hours later The anatomic observations were confined essentially to the urinary tract There was a crater-like ulceration of the anterior abdominal wall corresponding to the urinary bladder The edges of this crater were everted The lining of the crater consisted partly of mucoid, jelly-like material and partly of yellowish-green, necrotic material The interval between the pubic bones was 13 cm The penis measured 37 mm in length The dorsal surface was partly invaded by the crater-like ulcer About 9 cm above the growth, somewhat to the left, an opening of the left ureter was seen The left ureter measured 12 mm in diameter The right ureter was much distended, measuring 3 cm in diameter The lower end of the right ureter was invaded by the jelly-like growth On section of the growth, a honeycomb-like structure was seen There were also some cystic cavities which seemed to be filled with mucoid material No normal mucosa was demonstrated The edges of the growth were surrounded by skin The left kidney was considerably and uniformly enlarged and weighed about 250 Gm It was very firm in consistency The capsule stripped off easily On section a whitish, pale, rubbery parenchyma was seen The iodine reaction showed brown discoloration with specks and streaks The renal pelvis was slightly distended The mucosa was hemorrhagic and covered with turbid, greenish, purulent exudate An encapsulated mass, not unlike a kidney in shape, was seen at the upper end of the right ureter On cross-section, only a metastatic growth, 9 by 6 by 5 cm,

was seen. On section, it showed irregular cystic cavities filled with grayish-white jelly-like material. Both lower lobes of the lungs contained irregular larger areas of consolidation. On section of these areas, grayish granular tissue was seen. The areas were not air-containing. The spleen weighed 180 Gm., it was firm in consistency. On section, the typical picture of "sago" spleen was seen, with large mahogany-colored globules after the iodine reaction. Section of the edge of the crater showed the abrupt edge of a growth which consisted of smaller and larger cavities filled with amorphous secretion containing small round signet ring-shaped cells with peripheral nuclei. The secretion gave the microreaction of mucin with the special stain (thionine, polychrome methylene blue). Most of the cavities had no definite lining. The microscopic section of the lower end of the right ureter and of the mass at the place of the right kidney showed a typical picture. Sections of the left kidney showed advanced amyloid degeneration of the tubuli as well as of the glomeruli, which were filled with homogeneous masses of amyloid. In the spleen the amyloidosis was mostly restricted to the malpighian corpuscles. Sections of the lung showed bronchi and adjacent air spaces filled with masses of polymorphonuclear leukocytes and red blood cells.

CASE 2—Benign tumor of the renal pelvis of a "horseshoe kidney." V. C., a white man, aged 25, was admitted to the urological service of the New York Post-Graduate Hospital on Feb. 17, 1928, with a chief complaint of pain in the right groin and pyorrhea. Dissection of the pyonephrotic portion of the horseshoe kidney was performed by Dr. McCarthy. Grossly, this specimen had a bosselated appearance, covered with dense fibrous adhesions. It weighed 150 Gm. On section, the calices were cystically distended and filled with green purulent exudate. The upper calix contained a large impacted stone, forming a cast of the distended calix. A circumscribed growth, 35 by 25 by 13 mm., was situated at the upper orifice of the ureter. It had a honeycomb-like cystic structure and contained mucoid material. Section of the growth of the renal pelvis showed an abrupt change from the transitional epithelium to cylindric cells. The cylindric cells were mostly arranged in one layer. The cystic cavities were partly lined with these cells. In great part, however, no lining was seen. The cylindric cells were of the goblet cell variety, with marked mucoid secretion. The content of the cystic cavity, as well as the secretion of the cell, gave a typical mucin reaction (mucicarmine, thionine, polychrome methylene blue). All of the cells were of the typical differentiated mature type. No mitotic figures were found. The growth was well limited. There was a stroma which had irregular bundles of spindle-shaped smooth muscle cells, and there were larger blood vessels with thickened walls.

Tumors with mucus-secreting cylindric cells are rarely derived from the lining of the urinary tract. There are fifteen cases of mucoid carcinoma of the urinary bladder associated with ectrophy reported in the literature. Not a single case of circumscribed mucinous adenocystoma of the renal pelvis has yet been reported. Two explanations have been offered for the histogenesis of this type of neoplasm: (1) embryonal misplacement (Ehrlich, von Gelder, Keith, Hache, Judd, Plaut, etc.), (2) metaplasia following inflammatory changes (pyelitis cystica) (Stoerck, Enderlen, Klemperer, etc.). In most of the cases reported embryologic malformations were present. In the first case presented, the mucoid carcinoma of the bladder was associated with ectrophy of the bladder, hypoplasia of the penis, undescended testis (left) and cleft pelvis. The second case presented was surgical and only the horseshoe kidney is recorded. Adenocarcinoma of the bladder is rare and is commonly associated with ectrophy of the bladder. Embryonal misplacement of the intestinal mucosa not only is possible in the urinary bladder, which is a part of the cloaca, but also is possible along the ureter, which buds out from the cloaca. In the second case, no pyelitis cystica was present. In the adenocystoma of the renal pelvis only high cylindric cells with mucous secretion were demonstrated. They were arranged in one layer. No cells of the transitional epithelium type were present. Inflammatory reaction may be responsible for the differentiation and hyperplasia of the dormant embryonal cells. If the inflammatory reaction and stone formation were entirely responsible for this tumor, it ought to be found frequently.

Regular Meeting, Feb 27, 1930

LEILA CHARLTON KNOW, M.D., *President in the Chair*STUDIES IN ISOHEMAGGLUTINATION ALEXANDER S WIENER, MAX LEDERER
and S H POLAYES

In table 1 is presented the results of an analysis of the maternal blood and of the blood from the umbilical cord in a series of 500 cases. It will be seen that the blood from the cord has been classified under the four classic, fully established groups O, α β , A, β , B, α , and AB, α , and five subdivisions, O, α , O, β , A, α , and B, α . These five subdivisions do not represent any new

TABLE 1—*Results of Analysis of Maternal Blood and Blood from the Umbilical Cord*

Group of Mother	Number of Cases Examined	Number of Children									Incompatibility	
		O, α	O, α	O, β	O, $\alpha\beta$	A, α	A, β	B, α	B, α	AB, α	Number of Cases of Cord Serum Agglutinating Cells of Mother	Number of Cases of Mother's Serum Agglutinating Cells of Child
		O, α	O, α	O, β	O, $\alpha\beta$	A, α	A, β	B, α	B, α	AB, α		
A β	200	26	0	25	0	70	50	19	0	10	0	29
O, $\alpha\beta$	187	25	11	5	72	22	25	11	16	0	0	74
B, α	84	11	7	0	0	16	0	12	31	7	0	23
AB α	29	0	0	0	0	15	0	8	0	6	0	0
Totals	500	62	18	30	72	121	75	30	47	23	0	126

TABLE 2—*Results of Examination of Ninety-Four Families in Which One of Parents Belonged to Group AB*

Group of Father	Group of Mother	Number of Families	Group of Children				Totals
			O	A	B	AB	
?	AB	60	0	47	27	19	89
O	AB	10	0	12	14	0	26
A	AB	5	0	0	1	4	5
AB	A	1	0	2	0	0	3
B	AB	7	0	3	10	4	17
AB	AB	2	0	1	0	1	2
Totals		94	0	62	52	28	142
Per cent			0.0	43.66	36.62	19.72	100.00

groups peculiar to the blood from the umbilical cord but incompletely developed blood groups. From table 1 it is seen that 217 of the 500 specimens of blood from the cord, or 43.4 per cent, presented fully developed groups. Of particular interest, however, is the fact that not a single case was found in which the mother gave birth to a child whose serum contained an agglutinin which could agglutinate the mother's cells. This is all the more striking since there were 126 cases in which the mother's serum could agglutinate the cells of the child.

A practical application of this observation is that in case of emergency a newborn child can be given a transfusion with the blood of its mother without previous grouping or cross-matching, as that would be analogous to the use of a universal donor. However, we would recommend always choosing a donor of the same group, particularly in repeated transfusions.

The Bernstein theory and the von Dungern and Hirsfeld theory of heredity of blood groups were discussed. One thousand three hundred and thirty-four mothers with 1,462 children were grouped in order to determine which theory was correct. Our statistical data prove the inaccuracy of the theory of von Dungern and Hirsfeld and fully support the Bernstein theory. In table 2 are

listed the results of the examination of 94 families in which one of the parents belonged to group AB. Not one of the 142 children in these families belonged to group O. Moreover, among 516 children of 485 mothers belonging to group O, not one child belonged to group AB. It is of interest to note that according to the theory of von Dungern and Hirsfeld, these combinations should have appeared in our series of cases more than thirty-four times. Our data therefore completely support the Bernstein theory and prove the inaccuracy of the theory of von Dungern and Hirsfeld. In view of the fact that Haselhorst and Kossovitch have found two cases that seem to constitute actual exceptions to Bernstein's theory, however, some slight modification of that theory may be necessary, such as postulating the occurrence of mutations or nondisjunction, or the existence of another factor.

The application of blood groups to medicolegal cases in which the identification of blood stains or the determination of paternity is necessary was discussed. The work of Landsteiner and Levine on the new agglutinogens, M, N and P was also discussed.

DISCUSSION

MAX LEDERER. It is indeed surprising that there has not been a greater application of this knowledge in medicolegal work. In talking with Dr. Bernstein two years ago, he told me that it was being employed extensively in Germany, especially in determining paternity. The use of the test has discouraged a great many accusations by women who have falsely accused men of being the father of their children, thus exposing them to perjury. Schiff, in an excellent review, emphasizes the value of the test in a case in which a person had been accused of murder, and in which the main evidence of the prosecution rested on some blood stains which were found on the clothes of the defendant. The latter claimed he had cut himself. The prosecution insisted that the blood was from the murdered man. Examination of the blood stains showed the blood to be in the same group as that of the defendant, and in a different group from that of the deceased. In speaking with several jurists on this point, they have all expressed a profound degree of ignorance on this subject, and, in an effort to popularize its value, we thought it would be of interest and value to present the work at this society.

ALEXANDER WIENER. When M and N, which have been recently described by Landsteiner and Levine, have been worked up sufficiently so that they can be used medicolegally with A and B, the chances of proving nonpaternity of an innocent man will be almost one of three. With A and B alone the chances are one of seven. Landsteiner and Levine are working on additional agglutinogens now, and in the future we may be able to recognize the correct parents in practically every case.

PHILIP LEVINE. With regard to Dr. Wiener's statement concerning the possibility of obtaining further instances of excluding paternity, there is new evidence as to the existence of many differences in human blood. This is derived mostly from serologic experiments with immune antihuman agglutinins and with atypical agglutinins found in a small number of human serums. More indirect evidence as to the individuality of human cells in general has been obtained from the results of transplantation, since it is known that only autotransplants are successful. Similar results for animal blood were already obtained by Ehrlich and Morgenroth, and more recently by Todd. The practical application of these results with human blood must await perfection of the serologic method.

CHRONIC ULCERATIVE COLITIS. REPORT OF VACCINE THERAPY. WILLIAM Z. FRADKIN and IRVING GRAY.

In a series of patients suffering from chronic ulcerative colitis the Bargaen diplococcus was isolated from the colonic ulcerations in twelve of fifteen patients. Three failed to show the Bargaen diplococcus after repeated bacteriologic study. Material for culture was obtained by inserting a long, sterile swab through the

sigmoidoscope and scraping the depths of an ulcer. This material was immediately transferred to warm dextrose broth and incubated for about six hours. This was then subcultured in other tubes containing dextrose broth, and finally litmus lactose and blood agar plates were poured with material from the last culture tubes. The typical colonies were fished out and transferred to warm dextrose broth. The diplococcus fermented dextrose, lactose, saccharose, maltose and occasionally mannite, but never inulin. It was not bile-soluble. Vaccines were made containing approximately two billion organisms per cubic centimeter. The organisms were agglutinated by the patient's serum in each case. Intravenous injections of a pure culture of the diplococcus into rabbits produced lesions in the large intestine similar to those found in the human being. The submucosa of the gut showed myriads of the diplococci.

After eight injections of the vaccine, ten patients showed immediate improvement. The number of stools decreased rapidly and a gain in weight was noted in each case. Vaccine therapy was continued in certain cases for more than four months. One patient revealed a pure culture of the Bargaen diplococcus in nasal and tonsillar smears. Two patients did not respond to vaccine therapy. Improvement was noted more often and sooner and was more lasting when specific treatment was supported with rest, fresh air, small transfusions of blood, high caloric and high vitamin diets, and the irradiation of all possible foci of infection.

DISCUSSION

M. A. KUGEL. Does this organism ferment esculin, and have you differentiated it from the ordinary enterococcus?

WILLIAM Z. FRADKIN. It has not been tried.

PERRY MANHEIMS. Were these organisms submitted to the heat-resistance test? In practically every case in which we have made examinations of the stools and proctoscopic examinations, we have found an enterococcus which corresponds to the Bargaen bacillus in every way, except in regard to the heat-resistance test, the Bargaen bacillus is not heat-resistant, while the enterococcus is heat-resistant. We have also found the Bargaen bacillus in one instance in which there was no evidence of ulcerative colitis in practically pure culture.

WILLIAM Z. FRADKIN. We have not tried the heat-resistance test. The Bargaen diplococcus differs from the enterococcus in that it is bile-insoluble and does not ferment inulin. We were not fortunate enough to find the diplococcus in practically pure culture in patients not manifesting any signs or symptoms of chronic ulcerative colitis. The object in presenting this work tonight was to report the marked improvement obtained in patients with chronic ulcerative colitis by vaccines prepared with the Bargaen diplostreptococcus.

BILIARY AND HEPATIC FACTORS IN PEPTIC ULCER BENJAMIN N. BERG

Peptic ulcers were produced experimentally in dogs by excluding the flow of bile from the intestine. Three series of animals were studied. The first group consisted of seven animals with uncomplicated biliary fistulas. Acute duodenal ulcers were found in four of them. The second group included eleven animals in which biliary fistulas were complicated by biliary obstruction. Lesions were found in six animals. In three of these dogs, chronic duodenal ulcers were found, in one, a subacute perforated duodenal ulcer developed, in another, subacute ulcers of the duodenum and stomach were encountered, and in the sixth animal there were multiple erosions of the stomach and duodenum. The third group included five animals with complete biliary obstruction. Ulcers developed in three of the dogs in this series. In two animals chronic duodenal ulcers were found, and in one there were multiple gastric erosions.

The relationship of environment and diet to the incidence of ulcers was studied. It was found that lesions developed more readily under unhygienic conditions and with poorly prepared diets.

The mechanism by which the exclusion of bile predisposes the mucosa to ulceration depends probably on the loss of some constituent, such as mucus, which is essential for the preservation of an intact surface epithelium

The results of the investigation suggest the possibility that alterations in the function of the liver and in the secretion of bile may be important factors in the etiology of peptic ulcers. Although gross or microscopic changes in the biliary tract are found in only a small percentage of cases of peptic ulcer in man, nevertheless, functional disturbances which are not recognized by present inadequate methods may exist. The periods of remission and exacerbation that characterize so-called chronic ulcers may coincide with intermittent functional alterations in the stomach and duodenum in response to changes in the liver and in the biliary system

DISCUSSION

DAVID PERLA. This is an extremely interesting and suggestive piece of work. It has been the observation of various investigators working with suprarenal glands in animals that gastric ulcers have commonly developed following bilateral suprarenalectomy. We have had occasion to observe 500 rats with bilateral suprarenalectomy, and gastric ulcers developed in a high percentage of these animals. These observations were made incidental to other work. It would seem to me from what Dr Berg brought out that another explanation is possible to account for the appearance of gastric ulcers following surgical intervention in the biliary system. It is barely possible that in doing the operations they interfered with the nervous supply to the mucosa in those parts of the duodenum and stomach in which they found the ulcerations, and I would like to ask if that was carefully controlled. The same mechanism might hold true with the removal of the suprarenal gland, that is, an interference with the tonicity in regions in which these ulcers subsequently develop might effect the mucosa, with subsequent formation of erosions and ulcers.

PAUL W. ASCHNER. Ulceration of the stomach and duodenum has, of course, been produced by a great many procedures, but we do not know the cause of gastric and duodenal ulcer. Dr Berg's observation that the condition of the animal, the hygienic conditions and the feeding made great differences in the incidence of ulcers is important, because it adds weight to the belief that general factors come into play in the production of ulcers. It is well known that prolonged exclusion of bile from the intestinal tract has an injurious effect on the general body economy. For example, grave anemias and also osteoporosis have been noted after prolonged biliary drainage. I wonder whether any observations were made in these animals of the effect on the blood and bones as a result of prolonged exclusion of bile from the intestinal tract.

If disease of the gallbladder, or of the biliary tract, has a frank influence in the etiology of ulcer, we would expect to find ulcer of the stomach and duodenum much more common in women than in men, but the reverse is true. We find disease of the gallbladder and biliary tract common in women, and gastric and duodenal ulcer common in men. During the last year we have had three women on the wards of Mt Sinai Hospital who had coincident disease of the gallbladder and duodenal ulceration, so that it is possible in these particular patients that there may have been some relationship between the two conditions. Some experiments suggest themselves to my mind for definitely determining the role of the mucus from the gallbladder as a protective factor. Any information we may get concerning the etiology of ulcer is always welcome and interesting.

PAUL KLEMPERER. It seems to me that Dr Perla's suggestion is a good one. I feel too that some controls should have been mentioned of operative procedures in the same region, but without the production of biliary drainage. It occurs to me that we see frequently on the autopsy table postoperative biliary fistulas and complete obstruction of the common duct, even with occlusion of the pancreatic duct of long duration, and we fail to see ulcers in these cases. I saw

only recently one case in which there was a biliary fistula and obstruction in the ampulla of Vater with obstruction of the pancreatic duct. In this case there were multiple acute ulcers of the stomach. I have reviewed, in connection with this case, our entire material, and I found that this was the only case of its kind. Unfortunately, in this instance there was a severe infection around the pancreas with thrombosis of the artery and splenic vein, and it is most probable that the ulcers of the stomach were circulatory in origin. It is surprising that we do not encounter such instances of gastric and duodenal ulcers in man in whom obstructions of the common duct are so frequent.

MENDEL JACOBI. I should like to ask Dr. Berg if he noticed any difference in the degree of occurrence of pericholangitis and abscesses of the liver in the group of animals kept under the poor conditions downtown and in those kept under the better hygienic conditions prevailing uptown in the new medical buildings?

BENJAMIN N. BERG. Although numerous experimental methods have been employed to produce peptic ulcers, few investigators have been successful in producing chronic lesions. The ulcers which develop after bilateral adrenalectomy are usually acute lesions. Operative trauma played little role in the experimental procedure because the common duct was isolated without disturbing any of the adjacent structures. When the common duct is divided, the nerves accompanying it are severed. However, this had no etiologic significance with respect to the ulcers which were produced, because a similar procedure was followed in transplantation experiments without the formation of ulcers. Ulcers were never observed after bilateral division of the splanchnic nerves or after extirpation of the celiac ganglions. Although mild anemias were noted after the establishment of biliary fistulas, the changes in the blood were not marked and were associated probably with alterations in nutrition. Osteoporosis was not observed. Peptic ulcers are found associated with lesions of the biliary tract in man in a small percentage of cases. However, this does not preclude the possibility of the interrelationship between disordered function of the liver and peptic ulcer. The function of the liver may be disturbed markedly without gross changes in the biliary tract. In a series of cases of biliary fistulas in man, which were collected at the Presbyterian Hospital, peptic ulcers were encountered occasionally. Infection of the liver was found frequently whenever biliary obstruction existed for long periods. In animals with uncomplicated biliary fistulas, infection was usually absent. There was no relationship between the occurrence of infection of the liver and the environmental conditions.

SUBACUTE BACTERIAL ENDARTERITIS OF THE PULMONARY ARTERY ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS AND PULMONIC STENOSIS. HARRY GORDON and DAVID PERLA.

An instance is reported of subacute bacterial endarteritis (*Streptococcus viridans*) of the pulmonary artery associated with patent ductus arteriosus and pulmonic stenosis in which the valves showed no inflammatory changes. A boy, aged 13, with a congenital cardiac defect but in apparent good health developed an infection caused by *Streptococcus viridans* to which he succumbed within two and one-half months after onset. The clinical course was characterized by a septic fever, progressive weakness, secondary anemia and embolic phenomena in the spleen and kidneys. Autopsy revealed (1) a patent ductus arteriosus and a congenital pulmonic stenosis with marked hypertrophy of the right ventricle, (2) subacute bacterial endarteritis of the pulmonary artery and the ductus arteriosus with large thrombotic masses almost occluding the lumen, (3) no involvement of the valves, (4) embolic lesions in the lungs, kidneys and spleen, and (5) acute arteritis and arteriolitis of the small pulmonary vessels.

The direct relationship of congenital defect to bacterial inflammation is discussed.

SPLENOMEGALY DUE TO PORTAL THROMBOSIS SAMPSON J WILSON and MAX LEDERER

The patient, a boy, aged 2 years, had repeated severe gastric hemorrhages for a period of one year, necessitating many transfusions. His abdomen and spleen were large. A study of his blood showed it to be normal. He developed a peritonitis and sepsis before death. At autopsy the portal vein was found to be constricted just beyond the junction of the splenic and the superior mesenteric veins, and the esophagus showed varicose veins at its lower portion. The spleen was the seat of a chronic splenitis. Microscopically the portal vein showed a fibrous thickening in all three coats with a distorted elastica, which was destroyed in places—a typical phlebosclerosis.

Two additional cases with similar clinical courses were reported. Splenectomies were performed in these two cases, and both patients made uneventful recoveries.

The clinical course in portal phlebosclerosis, its etiology, pathology, differential diagnosis, prognosis and treatment were discussed and references to similar cases in the literature were given. The cardinal points on which the diagnosis should be made are the splenomegaly, the anemia, the signs of collateral circulation and the copious gastric hemorrhages which are followed by a diminution in the size of the spleen.

Photomicrographs of the lesion in the portal vein were shown.

DISCUSSION

A. A. EISENBERG. Under Dr. Hauswirth's guidance during the past six months we have begun a systematic study of the veins. About six months ago there was admitted to the surgical service of the Sydenham Hospital a man, aged 32, who had been acutely ill for a week with edema of the feet, enlarged spleen and liver, and who complained of severe upper abdominal pain on the right and left side. His temperature was between 100 and 101 F. The surgical service to which he was admitted considered the diagnosis of an intra-abdominal infection, or the possibility of a hypernephroma on the left side, and Dr. Hauswirth paid especial attention to the superficial veins in his arms, which were found to be tortuous and hard. They felt as a sclerotic artery would feel. Because of these observations on the superficial veins Dr. Hauswirth made a diagnosis of portal thrombosis, thinking the process was on the basis of a diffuse phlebosclerosis rather than an infection, of which there was no history. A superficial vein was taken out for examination. This proved to be a phlebosclerotic vein showing no evidence of inflammatory changes or degeneration, but rather a replacement fibrosis. The abdomen was opened, and no hypernephroma was found. The liver and spleen were greatly enlarged. The patient died on the third or fourth day after operation and at autopsy, thrombosis of the portal vein, both of the main stem and of the portal branches, was found. A thrombus was also found in the left iliac vein, and an enlarged spleen showing evidence of degeneration, was present. The sections from the portal vein showed what we thought were typical phlebosclerotic changes. In looking up the references to the condition, we found that phlebosclerosis occupied a place in pathology which might be called the stepchild of pathology. We could get little information about phlebosclerosis, the prominence being given to varicose veins, phlebitis, etc. We went to the earliest works and found that the incidence of phlebosclerosis pathologically was regarded as unknown. Etiologically, there is the opinion that it is a senile degeneration (Lobstein), while Sacks believed it to be a general disorder of nutrition, and it has also been regarded as an inflammatory condition (Fischer, Koestner).

These changes were found within the last six months in a rather small medical service, there were twenty-two cases in which the superficial veins, both in the arms and in the legs especially around the ankles, presented the same macroscopic and microscopic picture. An interesting phenomenon is that they all seem to have a fairly uniform condition associated with them. Sixteen of our twenty-two patients gave a definite history of gastric ulcer, they all seem to have a heart

which is rather smaller than usual. On the basis of what we have seen so far, we believe that these changes are neither degenerative nor inflammatory. They seem to occur especially in persons between 30 and 40 years of age, only two patients being past 40, and the remaining ones between 28 and 40. They seem to be symptomless, and without any definite etiology. The extent to which they may be symptomless is shown by a case of Buerger's disease which we have in the hospital. We removed a piece of vein from the good leg, and that is completely thrombosed, showing the same fibrotic changes, subendothelial thickening of the intima and replacement fibrosis of the media. Only a week ago Dr Hauswirth and I came across two articles written twenty-five years ago by Martin and Meekins and by Martin and Tull from Montreal. They examined children and adults, and claimed that they found phlebosclerotic changes in more than 30 per cent of their cases.

PAUL KLEMPERER. I think the importance of changes in the portal circulation causing splenomegaly cannot be overemphasized. During the last three years I have performed an autopsy in not less than six cases of splenomegaly in which the condition was laid to "Banti's disease," but was due to an embarrassment of the portal circulation. One of these cases showed an obstruction in the splenic vein alone, in the other five the portal vein was the main site of the lesion, there was occlusion in five cases, and merely a severe sclerosis of the portal vein in one case. The pathogenesis of changes in the portal system is simpler, I think, in children than in adults. In adults there is a multiplicity of causes which can cause such an occlusion of the portal vein, among which, of course, inflammation of the wall, thrombosis, and pressure from without play the main rôle. In children I would be inclined to consider mainly inflammatory changes in the portal vein as the cause of the subsequent either narrowing or complete thrombotic occlusion. That no history of an umbilical infection can be elicited in some of these cases, as in Dr Wilson's case, seems to me not to be convincing proof that there was not one present. I remember cases, one particularly, in which I found even an acute suppurative phlebitis of the umbilical vein in a new-born child with characteristic abscesses in the liver without any clinical evidence of umbilical infection, though it was looked for. I think therefore that a milder infection of the umbilical vein can be easily missed but may lead, nevertheless, to a productive phlebitis of the portal vein.

I believe phlebosclerosis, particularly of the portal vein, is a condition which must have a definite histologic picture. Phlebosclerosis was first described by the early authors but was studied in detail by Borrmann and later on by Simmons. I have studied a number of cases of phlebosclerosis, particularly in cirrhosis of the liver, and I have thought the changes in the vessel wall are similar to the changes in arteriosclerosis. One of the main features of a phlebosclerosis of the portal vein is the lamellation of the internal elastic layer, this I have seen definitely in cases of cirrhosis of the liver, and in the one case of splenomegaly I have mentioned before. My other five cases are divided and had different pathogeneses. During the last weeks I have again observed one case of thrombosis of the portal vein with canalization of the lesser omentum with so-called cavernomatous transformation. The patient in this case had a severe inflammation of the portal vein and of the superior mesenteric vein. The etiology was not clear. The patient had a four plus Wassermann reaction, but there were no other syphilitic changes. Simmons considered nearly every case of portal phlebosclerosis syphilitic in origin. I think this is exaggerated, and I cannot subscribe to it. The patient in this particular case had gangrene of one toe, which was clinically considered to be a thrombo-angitis obliterans. One has to consider that thrombo-angitis obliterans with its concomitant migrating phlebitis might be an etiologic factor in the causation of portal thrombosis. I should like to mention two more points. One receives frequently an enlarged spleen in the surgical pathologic laboratory from which the condition has to be diagnosed by the histologic picture alone. I think one peculiar feature is characteristic for splenomegaly due to embarrassment of the portal circulation, and that is the enormous increase in the sinuses of the spleen, the

hyperplasia of the sinuses which one sees in these cases. During recent years Duerk presented the sinus hyperplasia as one of the true criteria of "Banti's disease." I do not think it is actually so. If there exists such an entity as 'Banti's disease,' the sinus hyperplasia is not one of its characteristic features. If there is no evidence of inflammation in the spleen and mainly the sinus hyperplasia, I should suggest an embarrassment of the portal circulation as the cause of the splenomegaly. One question remains in regard to the treatment in these cases. Take the instances in which one suspects an embarrassment in the portal circulation. If there is an embarrassment in the portal vein proper, I do not see any reason for a splenectomy. Perhaps one would prolong the life of the patient for a short while perhaps one would shorten it, but if there is a definite evidence of occlusion of the splenic vein, I think splenectomy might be the rational treatment. Of course a surgeon can never tell us whether or not there is any embarrassment in the portal circulation because even with the best exposure, he does not reach the portal vein so well that he can definitely make a statement about its condition, particularly when the embarrassment is not due to actual thrombosis but only to phlebosclerosis. I have tried at the autopsy table to realize by palpation whether there was a change in the wall of the portal vein, and I could not do it in cases in which the microscopic examination revealed definite changes.

LOUIS HALSWORTH. Dr. Eisenberg did not emphasize the suggestion that we have made about the value of this particular work. It is more or less a rediscovery, so to speak, and the clinical significance is being studied. In one case a diagnosis of probable phlebosclerosis of the portal vein was made because the veins in the arms and legs were hard and almost completely closed, the veins had lost their normal color and looked like white cords. I call your attention particularly to that feature. Veins in the lower extremities are more frequently involved than the others. These veins, even at the time of excision, look like anything but veins. They are veins in which the lumen has almost completely disappeared. This particular patient had that condition in his superficial veins to an exquisite degree. The portal veins showed the same condition. The hepatic veins and the portal circulation likewise showed it. The iliac vein was a striking feature of the same lesion. What we want to emphasize is that this condition is not local, it is generalized. Just as the arteries do not give symptoms unless there is something added to the change in the vessel, so the veins give no symptoms unless infection or injury occurs which makes inflammation possible. Our patient had degeneration of the liver. All the veins took part in this general process.

We chose patients who had a peculiar type of build, more or less the asthenic type, somewhat cyanotic, with dropped and small hearts. These patients had ulcer of the duodenum or of the stomach. The possible causal relationship of these lesions is particularly what concerns us. In the first place, we know that the veins and arteries are thrombosed and fibrosed in cases of ulcer of the stomach and duodenum, and it is curious that this observation should not have attracted more attention. I said at the time that varicose ulcers of the leg resembled very much the ulcers one sees in the stomach and duodenum. At present we have a boy, aged 19, with an ulcer of the leg of two and a half years' duration which will not heal, and the ulcer looks exactly as a peptic ulcer would look, without any tendency to healing. All his veins partake of the sclerotic nature. The point I wish to make is that these patients with digestive ulcers also show the same lesions in the veins. Another curious case was one of Buerger's disease of five years' duration in a man, aged 26, in whom the toes of one foot were gangrenous. There were no changes to indicate any lesion of the vessels in the apparently normal leg, and yet a large vein was completely thrombosed, the walls thickened and the thrombus completely canalized. There is nothing inflammatory about these changes in the veins, and it is only in the hope of arousing more interest that we want to emphasize the relationship of gastric and other lesions to a generalized phlebosclerosis. These cases occurred in young persons. In none of them do we find the characteristic changes of arteriosclerosis. We had twenty-two cases, and

in none of the excised veins did we find a condition analogous to arteriosclerosis, and we have therefore suggested the name phlebofibrosis instead

MAX LEDERER In relation to splenectomy, I do not believe that one is advised to treat the condition in the portal vein. Splenectomy is advised in order to prevent, if possible, the hematemesis which may occur, especially after the inflammatory process in the portal vein has ceased. It is conceivable that there may have been an inflammatory process with narrowing of the lumen of the vein, and therefore a portal insufficiency. By removing the spleen, that load is taken from the portal vein, and it is possible that these patients may survive because a great many of them do die from esophageal hemorrhage. Only two weeks ago I performed an autopsy in a case of syphilitic aortitis with marked interstitial changes in the lungs, and the right and left sides of the heart were hypertrophied. The subject had a spleen which weighed 350 Gm, adherent at the upper pole, with a thick vascular omentum. We thought at first that the splenic enlargement was due to the syphilitic process, and we found we could not enter the portal vein. It was represented by a fibrous cord, and only after a great deal of care and dissection were we able to pass a fine probe into the portal vein. I think this was one case due to syphilitic infection. In the literature syphilis, syphilis and syphilis is mentioned, the idea being that most of the cases are of syphilitic origin. I believe as far as the phlebosclerosis of the portal vein, or the pyelophlebosclerosis, as it is called, goes, that it may be a local condition. There is no evidence of any other change in the vein. I want to say in conclusion, which I think I can say without hurting the modesty of Dr Klemperer, that the original diagnosis of the possibility of thrombosis of the splenic vein in the case reported by Dr Wilson was made by Mrs Klemperer

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Feb 10, 1930

HENRY C SWEANY, *President, in the Chair*

THE STRUCTURE OF THE LUNG AND ITS IMPLICATIONS IN INFLAMMATION OF THE ORGAN WILLIAM BLOOM

Evidence is presented that the respiratory portion of the lung is primarily of mesenchymal nature and that the so-called alveolar epithelium and the non-nucleated plates probably do not exist. The respiratory portion of the lung reacts in inflammation like a purely mesenchymal tissue, that is, by the exudation of hematogenous exudate cells and by the much slower mobilization of pericapillary mesenchymal cells. Inflammation in this organ thus affords a denial of those theories which explain the presence of all of the exudate cells in inflamed tissues as being of purely histogenous origin. This subject will appear in more detailed form as a part of a chapter in Maximow's "Textbook of Histology"

SYMPTOMATIC AND PATHOLOGIC OBSERVATIONS ON ANIMALS INOCULATED WITH THE VIRUS OF POLIOMYELITIS PAUL H HARMON

In tests to determine the susceptibility of a number of species of mammalia to parenteral inoculation of the virus of poliomyelitis, a sporadic incidence of suggestive symptoms and of suggestive cellular accumulations in the central nervous system was observed.

Virus, the potency of which was established by parallel inoculation into *Macacus rhesus* monkeys, when introduced into eighteen young rabbits by the combined intraperitoneal intracerebral method, resulted in the death of eight rabbits, and the appearance in three others of symptoms suggestive of prostration, convulsions

and transient motor pareses. Similarly, of seven young rabbits inoculated with normal monkey brain emulsion, none of which showed symptoms, two died.

When an emulsion of brain and cord removed aseptically from a number of rabbits which had died following inoculation of monkey passage virus was introduced into other rabbits (twenty-three in all) death followed in the second, third and fourth series of rabbits, thus simulating virus transfer from one generation to another. Eighteen of these rabbits died, and one showed suggestive symptoms. At the same time seven of nine rabbits inoculated with normal rabbit brain emulsion succumbed. None of these showed symptoms. It was shown, however, that no poliomyelitis virus was involved in these transfers, because rabbit brains of three different passages, in five instances, failed to induce poliomyelitis in monkeys, although inoculated intraperitoneally and intracerebrally in large quantities.

Over the same time, in thirty-eight uninoculated young rabbits, kept under similar conditions, twenty-one succumbed spontaneously, seven of which were observed to have died in convulsive seizures with symptoms identical with those seen in rabbits inoculated with virus. This correspondence in symptoms and mortality rate in the three groups of rabbits indicated that some other factor than the transmission of poliomyelitis virus from rabbit to rabbit was operative, which in all probability was miscellaneous intercurrent infections and infestations, since gross lesions of sufficient magnitude to have caused death were demonstrable in about 75 per cent. Among these lesions were disseminated and localized coccidiosis, tape-worm larvae infestations, bronchopneumonia with edema and hemorrhages into the lungs and hemorrhages into the large bowel.

Microscopic lesions suggestive of poliomyelitis were found in the cerebrum and spinal cord chiefly in the gray matter of four of forty-one rabbits inoculated either directly or in passage experiments with virus, and consisted of focal and perivascular accumulations of mononuclear cells. In the spinal cord there was often, in addition, a disseminated increase in cells in the gray matter. The most suggestive lesions were observed in the spinal cord of a rabbit which had shown no motor symptoms, but which was killed for examination. In a series of twenty-six uninoculated rabbits, dead spontaneously—with or without symptoms—or chlorotormed when apparently in perfect motor coordination, similar microscopic lesions were found in four. No perivascular collections of cells were found in the latter series, and neurophagocytosis was absent in all.

Of eleven dogs inoculated with poliomyelitis virus in three successive experiments, but two succumbed. At the same time, three of seven dogs that were inoculated with normal monkey brain emulsion succumbed. No symptoms were observed at any time in the animals that survived. Similar observations were obtained among uninoculated control animals. Postmortem examinations of the fatal cases showed bronchopneumonia of the lungs, while both in these animals and in many others that showed no effects following inoculation, no alterations were found in a carefully conducted search through many levels of the central nervous system.

Three of twelve young cats inoculated with virus succumbed, while among five controls receiving normal monkey brain none succumbed. No symptoms were observed in animals that lived. Gross pathologic examination, confirmed by microscopic methods, showed that when death occurred it was due to acute respiratory disease. Microscopic observations extended to many levels of the central nervous system, both in the cats dying from respiratory disease and in those killed following an uneventful five week observation period, failed to demonstrate changes.

Three diversified experiments with poliomyelitis virus on twenty-five guinea-pigs resulted in the death of thirteen of these animals. Among fifteen controls receiving normal monkey brain, three succumbed. In most of these, examinations showed that death was due to acute respiratory disease. Careful search in many microscopic sections of the central nervous system failed to reveal changes that might be interpreted as those of poliomyelitis.

Among thirty-two white mice inoculated with virus, ten succumbed in the five week observation period, while among thirty-one mice inoculated with normal

monkey brain, seven succumbed in a similar period. No symptoms suggestive of flaccid motor paralysis were observed in any of these animals. Gross pathologic observations established the cause of death in a majority of instances as due to acute respiratory disease.

Of four young pigs inoculated with massive doses of virus, none showed symptoms. Two young pigs receiving normal monkey brain showed no symptoms during the observation period.

Two of four lambs inoculated with virus developed suggestive motor incoordination, but this was due to the concomitant general prostration of pneumonia. No symptoms were observed in control animals. No alterations were found in the central nervous system of the affected animal.

Two of three calves succumbed following inoculation with virus, but no alterations could be demonstrated after a careful examination of the central nervous system.

Conclusions—1 In attempts to transfer poliomyelitis to young rabbits, with virulent monkey passage virus, occasionally death, sometimes with suggestive motor symptoms, was observed. Young rabbits were shown to be markedly susceptible to intercurrent infections and infestations.

2 Convulsive seizures and other motor symptoms, as well as certain cellular changes in the central nervous system of rabbits inoculated with poliomyelitis, are nonspecific, identical symptoms and cellular infiltrations being observed both in rabbits inoculated with normal rabbit brain and normal monkey brain, and in uninoculated young rabbits.

3 Young dogs, young cats, guinea-pigs, mice, young pigs, lambs and calves do not develop any condition recognizable as, or related to, poliomyelitis following massive inoculation of virus of established pathogenicity for monkeys. Although a small proportion of inoculated animals succumbed, death is due, in the main, to acute intercurrent respiratory disease.

TUBERCLE-LIKE STRUCTURES IN HUMAN GOITERS R. H. JAFFE

In three nodose goiters and in one diffuse goiter with mild hyperthyroidism there were found in the removed thyroid tissue nodular structures composed of epithelioid cells and giant cells which resembled miliary tubercles. The origin of the cells could be traced to the follicular epithelium. The patients had no other signs of tuberculosis and made an excellent recovery. Tubercle bacilli could not be demonstrated in sections nor in the sediment obtained by dissolving a great many frozen sections with the aid of antiformin. There was no caseation in the nodules but much fibrous tissue about them.

The literature contains numerous reports on benign miliary tuberculosis of the thyroid. It is questionable, however, whether all these cases are really tuberculous, because in most of the reports there is no support of this diagnosis other than the microscopic similarity with miliary tubercles. The explanation is advanced that tubercle-like structures may result from noninflammatory involutional changes of newly formed or old follicles of the thyroid. These changes should be separated from true tuberculosis of the thyroid and from tuberculous goiters.

PULMONARY SIDEROSIS TWO CASES WITH RETICULO-ENDOTHELIAL SIDEROSIS MILTON G. BOHRD

Two cases of pulmonary siderosis are reported, in one in which the dust was metallic iron, the black variety of siderosis was produced and ended in a florid tuberculous bronchopneumonia, in the other, in which the dust was iron ore, the siderosis of the red variety and the concomitant tuberculosis were of the fibrotic type and limited to the lymph glands.

In both there was a continuous attempt at excretion of the iron by macrophages which carried it into the alveoli, thence into the sputum, by excretion through the bronchiolar mucosa, or by transference to the lymph nodes. In the latter

event, the pigment either was deposited in the gland or was carried through the gland and reached the blood stream probably by way of the thoracic duct. Having reached the blood stream, the iron was deposited in the cells of the reticulo-endothelial system.

In addition to transportation there was gradual transformation of the iron. Only the soluble iron could be transported and was found intracellularly. In the black variety, where more silicon than iron was present in the lung, only the more soluble iron found its way into the blood stream. Insoluble iron was found extracellularly in dense fibrous tissue.

Where the accumulations of iron were greatest the amounts present were 8.9 and 7.9 per cent of the moist weights of the lungs.

The chemical examination of the sputum for iron may be an aid in the clinical recognition of siderosis.

DETORSION DEFECTS IN CONGENITAL CARDIAC ANOMALIES. REPORT OF THREE CASES, WITH AN ANALYSIS OF THE MECHANISM OF THEIR FORMATION. PHILLIP F. SHAPIRO

This article was published in full in the January issue of the ARCHIVES.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Feb 13, 1930

BALDWIN LUCKE, *Presiding*

INFLUENCE OF AGE ON ANTIBODY FORMATION. JULES FREUND

Immunity conditions in very young and in adult animals differ considerably. This difference may invalidate conclusions formulated without taking into consideration the influence of age on immunity conditions.

It is known that hypersensitiveness to the intracutaneous injection of tuberculin is not transmitted from tuberculous female guinea-pigs to their offspring. This fact has been used as one of the chief arguments for the view that antibodies play no role in the intracutaneous tuberculin reaction. This argument is not valid in the light of the demonstration that the skin of young tuberculous guinea-pigs is quite refractory to the injection of old tuberculin during the first month after birth (*J. Immunol.* **13** 285, 1927, **17** 465, 1929).

In rabbits less than 20 days old, the formation of agglutinins against typhoid bacilli, of hemolysins against sheep cells and of precipitins against horse serum and egg white is strikingly less intense than in adult rabbits immunized in the same way. A definite Arthus phenomenon cannot be produced in young rabbits immunized with horse serum or egg white.

SYSTEMATIC ANALYSIS AND CLASSIFICATION OF SKIN TESTS. HERBERT FOX

Contradictory and irregular skin reactions to the toxins and emulsions of streptococci in certain diseases such as arthritis, endocarditis and nephritis, dictated the need of analyzing the facts known about all the groups of skin tests. They are tabulated and analyzed numerically. They are found to fall into four rough groups, in which the following combinations are indicated:

Anaphylaxis, Schick and Dick tests fall together, tuberculin and typhoid are close but not identical, and animal parasites are numerically the same as the last two. These five are distinct from the natural serum, epidermal, pollen, drug and dust sensitivities. Food sensitivity belongs in an entirely separate group.

The inconsistency of the whole tabulation indicates a weakness in the knowledge of the mechanism, that the antigen and test are less important than the bodily mechanism, and that the constitutional basis is perhaps the most important of all

It will be necessary to have a knowledge of normal cutaneous responses, capillary permeability, simple chemistry and physiologic chemistry before a real standard of skin response can be established. To this end, it may be possible to create a standard and norm per individual by the use of a previously standardized quantity of histamine at each injection for skin test purposes

CRITIQUE OF THE BACTERIAL SKIN TESTS, WITH A SPECIAL REFERENCE TO STREPTOCOCCI MACKINNON ELLIS

The interpretation of bacterial skin tests is complicated by variations in technic and by lack of understanding of the mechanism. Technical differences may lead to complete disagreement of results. The conception of the toxic reaction has over-reached itself and has led to much misinterpretation

A true toxic reaction must be neutralizable by immune serum, not passively transferable and thermolabile. Negatives are due to antitoxin and to individual hyporeactivity

The Schick, Dick and *Streptococcus erysipelatis* reactions are apparently true toxic reactions, whereas the so-called toxic reactions of various streptococci fall better in a group with the tuberculin reaction. The typhoidin reaction and pseudoreaction to the Schick test also fall in this group

Animal experimentation shows that rabbits can be made skin reactive by inoculation with streptococcus preparations. Desensitization can be accomplished by the intravenous method only. There are four kinds of response: normal, hypersensitive, immune and cachectic

The relation of streptococcus skin testing to disease is discussed, but no conclusions could be drawn, since the underlying mechanism is not known

LYMPHATIC PERMEATION STRIKINGLY ILLUSTRATED IN A CASE OF CARCINOMA PROBABLY PRIMARY IN THE THYMUS GEORGE M ROBSON

Lymphatic permeation is commonly observed in carcinoma. The following case is of interest because it presents such a striking picture of this mode of dissemination. The case is also of interest because of the probable thymic origin of the tumor

The patient was a white man, aged 53, admitted to the University Hospital because of cough, vomiting and difficulty in swallowing. He was blind in his right eye. The dysphagia was largely paralytic, and there were other evidences of paralysis of the tenth and twelfth cranial nerves. The duration of illness was about six months, with severe symptoms developing rapidly during the last few weeks of life. On admission the patient was dehydrated and emaciated, having lost 45 pounds (20.4 Kg). He passed rapidly into a semicomatose condition, and died suddenly a few days after admission

At autopsy, 600 cc of clear fluid was found in the right pleural cavity. The pericardial sac contained 620 cc of bloody fluid incident to a fibrinosanguineous pericarditis. The mediastinum was extensively involved by a neoplastic process which extended to the pericardium, left lung and pleura. The thymus was moderately enlarged, weighing 35 Gm. It was firmer than normal. On section, the surface was found to consist largely of grayish-white tumor tissue, a number of fibrous trabeculae and adipose tissue. Its outline was preserved, and it could be separated from the surrounding structures with a fair degree of ease, although it was somewhat adherent. The surrounding tissue was infiltrated, with involvement of the lymph nodes, especially of a group around the hilus of the left lung and a chain extending up to the right side of the neck

The tumor extended into the left lung as large cords of soft white material in dilated lymphatics about bronchi and blood vessels. On the pleural surfaces

it formed a network of white cordlike elevations outlining the lobules. Both layers of the pericardium were partially covered by fibrin and showed extensive infiltration similar to that seen in the left lung. Just back of the pericardial sac, between it and the lower portion of the esophagus, there was a layer of moderately firm, whitish tumor tissue 1.5 cm in thickness. In the adjacent muscular wall of the esophagus, there were two nodules of similar appearance, the larger measuring 4 by 3 by 2.5 cm. The mucosa was intact and movable over both, but the larger nodule caused a partial compression stenosis. Two enlarged lymph nodes were seen in this region. The only noteworthy lesion below the diaphragm was a nodule 6 mm in diameter in the left suprarenal gland.

The brain showed flattened convolutions. Everywhere, but especially over its base the pia was thickened and whitish. On section 20, soft grayish-white tumors were found within the brain, varying from 2 or 3 mm to 3 cm in diameter. The larger ones were in the cerebellum. Most of these were obviously in continuity with the thickened meninges, representing an extension into the brain from the meningeal involvement in deep sulci.

Histologically the tumor everywhere was composed of a large epithelial type of cell with an abundant, slightly basophilic cytoplasm. These occurred in sheets, masses or cords with very little or no stroma other than that of the preexisting tissue. Their nuclei were quite large and prominent. The chromatin in them was arranged into a coarse reticulum. Most of the nuclei contained large eosinophilic nucleoli. Mitotic figures were numerous. Nowhere was there any prickly cell formation or keratinization.

The thymus showed the most advanced type of involvement. Sections from it were composed of almost solid cellular tumor areas. The thymic tissue was reduced to small accumulations of lymphocytes, with occasional small adipose areas. Only occasional Hassall's corpuscles were observed. From the carcinomatous areas, strands of tumor cells extended into the surrounding tissue, usually in the lumina of definitely recognizable lymphatics, frequently accompanying blood vessels.

The invasion of the esophagus was limited to the muscularis and submucosa, and consisted of cords and strands of cells infiltrating between the bundles of muscle fibers, many of which were atrophic. Necrotic changes were present in the central portions of the nodules. Many widely dilated lymphatics containing cords of tumor cells were present at the outer edge of the tumor in the muscular coat.

In the lung the tumor seemed to be confined entirely to the lymphatics, which were seen as thin-walled, endothelial lined spaces following bronchi or blood vessels and containing cords of tumor cells. They varied in size from that just wide enough to accommodate two or three cells, to several millimeters in diameter. In the larger ones, there was much central necrosis of the cells. The invasion seemed to be from the hilus toward the periphery of the lung, and in many places to reach the pleural surface. In the pleura there were similar widely dilated lymph spaces filled with partially necrotic tumor and producing the white network noted in the gross specimen.

Both layers of the pericardium were covered by a fibrinous exudate with beginning organization. It everywhere contained greatly dilated lymphatics filled with tumor cells. Here and there strands of these invaded the organizing exudate. At several points, strands of tumor cells accompanied the arteries deep into the myocardium.

The histology of the brain and meninges was spectacular. Everywhere the pia was infiltrated with cords, sheets, strands and masses of large epithelial cells. These followed the pial vessels as they descended into the brain substance, surrounding them with cylinders of tumor cells, evidently contained in the Virchow-Robin spaces. This process was most marked in deep sulci filled with tumor. Tumor masses within the brain connected with those in the meninges in this manner. The right optic nerve showed an extensive infiltration beneath its sheath, thus accounting for the blindness of that eye.

Book Reviews

BACTERIOLOGY, ESPECIALLY DETERMINATIVE BACTERIOLOGY By PROF DR K B LEHMANN and PROF DR R O NEUMANN Seventh completely revised edition Volume 1 Parts A and B, Technique and General Determinative Bacteriology Part C, Atlas Translated by Prof Dr Robert S Breed Price, \$7.50 Pp 172, with 3 text figures and 65 plates (63 in color) New York G E Stechert & Company, 1930

LABORATORY MANUAL OF BACTERIOLOGICAL METHODS By the same authors and translator Price, \$1.50 Pp 103, with 3 text figures and 5 colored plates New York G E Stechert & Company, 1930

During more than thirty years, many beginners in bacteriology have been guided by the atlas and manual of determinative bacteriology of Lehmann and Neumann, specialists have used it as a reference book, and taxonomists have fought over the system of classification of micro-organisms employed in it. This English translation of the seventh edition will undoubtedly extend the battle-line of taxonomic argument, place Neumann's beautiful pictures of bacteria in the minds of new beholders and continue to guide—and, unfortunately, also misguide—beginners.

The fundamental purposes of the first edition of 1896 and of succeeding editions have been both taxonomic and technical. The colored plates illustrating the volumes have supported both of those purposes, serving as checks on the results of procedures and as a vivifying illumination of the text. While many of the pictures of black medium with colonies or stab cultures crusted on the background seem stiff and unnatural, they have been and remain the unique feature of the work. They have lost none of their brilliance in this latest reproduction.

In the taxonomic field, Lehmann's influence has been on the side of conservatism. An inspection of this first volume shows that he has maintained that position. Recognizing the variability of bacteria, he has combined species and has created few new ones. He cautions the bacteriologist to remember that "variability of bacteria produces many difficulties for bacteriologists. For this reason he should never christen an organism as 'new' until he has determined that it is absolutely necessary." Classifications would be greatly simplified if the industrious nominators in bacteriology would heed this admonition. In this volume, Lehmann has used neither Bergey's classification nor his nomenclature. He uses trinomials like "*Bacterium tussis-convulsae*," designates the pneumococcus "*Streptococcus lanceolatus*" and gives the term bacillus to both spore-bearing aerobes and anaerobes. In addition, there is no evidence in this first volume that the significant modern studies of bacterial variation have been considered at all. While the first volume provokes these comments on an inferential estimate of the author's point of view, it is inadequate to serve as a basis for the examination of Lehmann's manner of dealing with these questions. It will be more appropriate to postpone that inquiry until the appearance of the forthcoming translation of the second volume, in which these matters will be considered in detail.

If one limits the examination to the specific content of the first volume, one discovers by the date of the preface, which is 1926, that the "seventh completely revised edition" is already in its fifth year. Neumann was unable to collaborate in the preparation of this edition, and when the work was made ready for the press in 1926, Lehmann was assisted by Dold, Sussmann and Haag. As these authors cite only a few references to the literature later than 1922, it is to be anticipated that much of the newer work in bacteriology will not be found within

the covers of this volume. Almost all the references are to publications in German. Many formulas of the habitually used mediums and well tried stains are given, and the fundamental steps to be taken in isolating and identifying bacteria are set forth in order. The procedures are of unquestionable utility, but the descriptions of them are not always as definite and precise as would be required by one who wishes to follow them exactly. References to the original sources are given in many cases, but there is little reference to the changes and improvements that have occurred with the passage of years. Many useful procedures are omitted, and in this volume serologic procedures are mentioned only by title, as they are to be described in volume 2. To a worker in this age of the facile hypodermic syringe, the setting is given an antique air when it is recommended that animals be "inoculated with a platinum loop."

The separate Manual is a verbatim reprint of the first 103 pages of the first volume and the first five colored plates. References to other plates in the first volume and to procedures in the second volume are given in a way that makes it seem unlikely that this section was intended to be exploited as a manual. It is doubtful whether it can, with fairness, be said to contain a "description of bacteriological technic commonly used in German bacteriological laboratories." In any case, manuals are usually such local directories that those which serve general needs are rare. The manuals may agree in general principles, but they vary according to the practices of the chiefs of laboratories of states, cities and schools. This manual has not the qualities of universality. It will be of little use to a bacteriologist in this country. Some of the advice to the beginner is actually misleading, as, for example, in the "Detailed example showing how bacteria are identified," on page 99. The case chosen for study is one of "eczematous conjunctivitis." It is said here that the finding of gram-negative, biscuit-shaped cocci and small, thick, regular-shaped gram-negative rods in the smear of the exudate "indicates that the cocci are gonococci and that the rods belong to the colon group." In fact, as there are often other gram-negative diplococci and rods in conjunctival exudates, this observation indicates and suggests more possibilities—and probabilities—than this bit of guidance for the beginner would admit. In paragraph *c* of this section, it is said to the beginner that "tubercular organisms" are excluded by the failure to find them in an acid-fast stain of the exudate of this eczematous conjunctivitis. The lamentable results of false conclusions have shown that the categorical negative is inappropriate in reporting smear diagnoses of exudates.

The translation remains to be considered. Opinion of the rendition of the German into English fluctuates with the sections read, as there is some variability. In many sections, the translator has produced a smoothly-flowing English, precisely presenting the meaning of the difficult technical German. In others, the construction remains somewhat Teutonic and there are mistranslations of words and phrases. "It is even more certain to sterilize in an autoclave," and "If colonies appear only as one or two" are examples of the few inverted constructions. Examples of mistranslations are "entire" for "glatt," as in the sentence, on page 102, "entire or very finely granular," where the description is that of a smooth or finely granular colony edge. The reviewer is not an expert in either the German language or the German comestibles. His curiosity, however, was aroused when he found on page 36 that pile worms (*Teicho*) may be used in place of lean meat in preparing a certain medium. The German word is "Pfahlmuscheln," and *Teicho* does not occur in the German text. Dictionaries sanction the translation ship-borer for Pfahlmuscheln. But it seemed such a laborious undertaking to dig the worms out of water-logged, worm-eaten timber in order to use them as a substitute for a piece of lean meat that the reviewer sought the advice of those who might have engaged in this sort of fishing to provide food for phosphorescent bacteria. He is informed by those who have eaten Pfahlmuscheln that the succulent animal referred to is the mussel, *Mytilus edulis*,

and not the burrowing *Teredo*. Twice the translation relapses into German, with an "und" and a hybrid "precipite."

As the book was printed in Germany, it is remarkable that so few words of this kind are found, and that there are only two or three typographic errors in the volume. The proof reading was done with great care. The good paper used, the clear typography and the excellent reproductions of the colored plates exhibit the attention to detail which the publisher devoted to the production of the volume.

Respect for the great and beneficial influence which Lehmann and Neumann, and their book, have had on systematic bacteriology, homage for Dr. Lehmann, who even after his seventieth year is still carrying on the struggle to lift bacteriology into the position as a science, and a sympathetic regard for the labor that has been devoted by the translator to the service of bacteriologists have made the writing of this review painful. With reluctance, the reviewer is forced to conclude that volume 1 of this work will be of little use to bacteriologists in this country.

S. BAYNE-JONES

THE PATHOLOGY OF THE EYE. By JONAS S. FRIEDENWALD, M.D., Associate in Pathological Ophthalmology at the Johns Hopkins University. Price, \$4.50. Pp. 346, with 253 figures, mainly photomicrographs from the Pathological Collections of the Wilmer Ophthalmological Institute and the Army Medical Museum, by Helenor Campbell. New York: The Macmillan Company, 1929.

This book should interest all who are concerned with the study of the diseases of the eye. It is not voluminous yet touches all important ocular disturbances. The book will be particularly valuable to the practitioner because the relation of clinical appearances to anatomic changes is emphasized on the basis of a study of ocular diseases through many years. It is well illustrated, and helpful references to the literature are given. The introduction reviews concisely the structure, physiology and pathologic anatomy of the eye and adnexa. Inflammations of the globe are then discussed. Excluding specific inflammations such as tuberculosis, syphilis and sympathetic ophthalmia, the inflammatory disorders of the eye are the most difficult to systematize. The author divides these into two categories, panophthalmitis and focal lesions of an acute or subacute character. One wonders if this division into general and focal types of ocular inflammation does not confuse more than it simplifies. The author does not distinctly differentiate the cellular changes of these inflammations as Fuchs does. The specific inflammations (tuberculosis, syphilis and sympathetic ophthalmia) are handled so well that the reader cannot but wish that space had permitted the author to write more fully about them. There is recorded an interesting observation of a myeloid type of infiltrating wandering cell in the eyes of stillborn syphilitic infants. The chapter on injuries is good. The knowledge of radiant energy is briefly but well presented. The introduction of a third form of glaucoma, subacute, seems superfluous and confusing. The different theories of glaucoma are briefly discussed, including the view now held regarding the relationship between the intra-ocular blood vessels and the aqueous humor.

Much may be said in favor of the author's grouping of clinical disorders of the eye into associated pathologic conditions rather than according to the usual anatomic arrangement. The grouping may give a better conception of those disorders which affect, in their progress, more than one structure of the eye. Glaucoma must always be taken up in this way, and the intra-ocular inflammations, both specific and nonspecific, are perhaps better so handled. The author's review of senile changes and arteriosclerosis in one chapter is appropriate. Injuries of the eyeball, hereditary anomalies and diseases of the eye, as well as tumors of the eye, lend themselves well to groupings involving all parts of the eye. Nevertheless, there is little question that pathologic anatomy as well as practical ophthalmology can be taught more systematically by adherence to the anatomic basis.

EDEMA AND ITS TREATMENT By HERMAN ELWYN, M D Price, \$2 50 Pp 182
New York The Macmillan Company, 1929

In this book one sees something of a reaction against the prevailing tendencies to put the problem of edema on a purely physicochemical basis solvable by test tube experiments with water and membranes, for Elwyn visualizes edema as something far more intricate and vitalistic. He starts out with a brief consideration of some of the prevailing theories of edema and water regulation, pointing out their shortcomings, and emphasizing the view that the maintenance of blood volume and water concentration is a vegetative function requiring adaptive regulatory mechanisms that have been developed phylogenetically. A discussion of the methods used by the body to keep the total blood volume and the water concentration of the tissue approximately constant leads to the conclusion that for such a complicated exchange process some central regulatory mechanism must necessarily exist. Since for other vegetative functions, the center of regulation seems to lie in the sub-thalamic and hypothalamic areas, working through the sympathetic and vagus, a similar center closely related to a center for salt metabolism is assumed to exist. It is assumed that discharges from this center, under the stimulation of changes in the water concentration of the blood passing through the center, cause alteration in a "constellation of electrolytes at the intersurface of the two phases in the colloidal system of the cell," which in turn affects the water content of the colloids.

Obviously this is a highly speculative theory which piles up more unknowns and undemonstrables as explanation of the original unknown but it nevertheless has value as emphasizing lines of thought not generally adequately followed by students of the problem of edema. That central influences may modify water metabolism is proved by the polyuria that results from lesions in the hypothalamic region, and hence one cannot leave out of consideration the influence of the central nervous system in discussing edema, as has too generally been done. Elwyn has brought together many interesting lines of evidence on which to build up his theory, and has made a distinct contribution to the literature of the fascinatingly involved subject of edema even though the presentation at times seems to have metaphysical qualities.

CLINICAL ASPECTS OF VENOUS PRESSURE By J A E LASTER, B Sc, M D,
Professor of Physiology, University of Wisconsin, Associate Physician,
Wisconsin General Hospital Price, \$2 50 Pp 135, with 7 illustrations
New York The Macmillan Company, 1929

As its title suggests, this monograph deals with rather a neglected phase of cardiovascular disease. The reviewer cannot agree completely with the author's concepts of the dynamics of heart failure. Nevertheless, the technic, normal controls and standards in various clinical disorders constitute an important addition to the diagnostic and especially the prognostic armamentarium of the clinician. The book emphasizes that alterations in the venous pressure commonly precede other peripheral manifestations of altered compensation of the heart. Although the book is meant primarily for clinicians, its fresh points of view make it worth reading by pathologists.

EXPERIMENTAL STREPTOCOCCIC INFLAMMATION IN NORMAL, IMMUNE AND HYPER- SENSITIVE ANIMALS⁴

B J CLAWSON, MD

MINNEAPOLIS

In experimental work previously reported,¹ it was shown that inflammation with a cellular reaction similar to that found in tissues in cases of human rheumatic infection could be produced by the injection of streptococci of low virulence in small doses into the myocardium and the subcutaneous tissue of rabbits. With larger doses, abscesses developed. In these experiments, it was not determined whether the type of reaction was influenced by existing immune or allergic reactions, since most of the animals had had injections of streptococci before.

The experiments reported in this paper were carried on in an attempt to determine what part, if any, allergy or immunity played in the pathogenesis of these experimental lesions.

The phenomenon of allergy as related to inflammation, came into recent prominence with the work of Swift and his associates² by the discovery of the secondary reaction produced in rabbits following the intracutaneous injection of streptococci isolated from subcutaneous nodules in cases of acute rheumatic fever. These workers decided that

⁴ Submitted for publication, Dec 22, 1929

¹ From the Department of Pathology, University of Minnesota

² Read before the American Association of Pathologists and Bacteriologists, New York, April 18, 1930

¹ Clawson, B J. Experimental Rheumatoid Myocarditis, *Arch Path* **2** 799 (Dec) 1926, Experimental Subcutaneous Rheumatic Nodules, *Am J Path* **4** 565, 1928

² Andrewes, C H, Derick, C L, and Swift, H F. The Skin Response of Rabbits to Non-Hemolytic Streptococci, *J Exper Med* **44** 35, 1926. Derick, C L, and Andrewes, C H. The Skin Response of Rabbits to Non-Hemolytic Streptococci, *ibid* **44** 55, 1926. Derick, C L, and Swift, H F. Hyperergic Tissue Response to Non-Hemolytic Streptococci, *Proc Soc Exper Biol & Med* **25** 222, 1927, Immune Tissue Response to Non-Hemolytic Streptococci, *ibid* **25** 224, 1927. Swift, H F, Hitchcock, C H, and Derick, C L. General Tuberculin-Like Reactions in Rheumatic Fever Patients, Following Intravenous Injections of Streptococcus Vaccines of Nucleoproteins, *ibid* **25** 312, 1928, Bacterial Allergy (Hyperergy) to Non-Hemolytic Streptococci, *J A M A* **90** 906 (March 24) 1928. Derick, C L, and Swift, H F. Reactions of Rabbits to Non-Hemolytic Streptococci, *J Exper Med* **49** 615, 1929

this secondary reaction was an allergic phenomenon of the nature of the reaction of the skin to tuberculin rather than the Arthus phenomenon. The rabbits giving the secondary reaction were considered to be hypersensitive to streptococcic protein. This hypersensitiveness was called the hyperergic state. It was found that hypersensitiveness or bacterial allergy seemed to accompany the production of focal lesions of a certain intensity, and that it was probable that in these foci the substances or conditions were produced that led to bacterial allergy. This hypersensitiveness to streptococci was produced and maintained by the injection of agar and streptococci subcutaneously into the rabbits. It was also shown that this type of bacterial hypersensitiveness did not follow primary intravenous inoculations of rabbits with comparable doses of streptococci. The hypersensitive state was manifested by ophthalmic, skin and lethal reactions that were produced by the injection of streptococci into allergic animals in doses small enough to have no effect on nonsensitized animals. By tests with streptococcic vaccines, many patients with acute rheumatic fever were found to be hypersensitive to streptococcic protein. This was also confirmed with skin tests on patients with rheumatic fever by Birkhaug.³ These experiments and observations are of interest because they suggest that the clinical condition called acute rheumatic fever is definitely associated with and possibly dependent on a hypersensitiveness of the patient to streptococcic protein.

Allergic inflammation has come to be considered by many as a specific anatomic type of reaction and is thought of as being synonymous with proliferative or polyblastic inflammation. Swift stated that the anatomic features of tuberculous and syphilitic inflammations had been thoroughly established as allergic in their pathogenesis. Maximow,⁴ in speaking of allergic inflammation, said "As far as one can judge by the still modest accumulation of facts available at present, the differences, as compared with the histogenesis of common inflammation, are quantitative rather than qualitative." Rich and McCordock⁵ offered objections to the idea that inflammation in persons or animals sensitized to tuberculo-protein had a specific characteristic. They were convinced that the inflammation occurring in the allergic state in association with tuberculosis showed a quantitative rather than a qualitative difference.

3 Birkhaug, K. E. Rheumatic Fever, Allergic Reactions with Toxin-Producing Strain of Nonmethemoglobin-Forming Streptococcus Isolated from Rheumatic Fever, *J. Infect. Dis.* **43** 280, 1928, Rheumatic Fever, Skin Hypersensitiveness of Patients with Rheumatic Fever and Chronic Arthritides to Filtrates, Autolysates and Bacterial Suspensions of Streptococci, *ibid.* **44** 363, 1929.

4 Maximow, A. A. Morphology of the Mesenchymal Reactions, *Arch. Path.* **4** 557 (Oct.) 1927.

5 Rich, A. R., and McCordock, A. H. The Pathogenesis of Human Tuberculosis, *Bull. Johns Hopkins Hosp.* **44** 273, 1929.

and that the anatomic type of reaction observed depended on the virulence, the number of organisms and the tissues into which the organisms were injected

The term allergy in this paper is used to mean a state of hypersensitivity to a bacterial protein. There is no attempt to explain the relation between allergy and immunity or resistance, but a study is made of the relationship of experimental foci of inflammation, streptococcic in origin, to hypersensitiveness and to a general immune state as indicated by agglutinins in the blood. The following experiments were performed in an attempt to learn whether the experimental inflammation in hypersensitive or immune animals was different from the inflammation in normal animals. If it is proved that animals hypersensitive to a bacterial protein respond to doses too small to call forth any reaction in nonsensitive animals and react with the same type of cellular reaction which is produced by larger doses in nonsensitive animals, this fact may help to explain why, in rheumatic patients who have been found to be hypersensitive to streptococci, such extreme reactions take place when obviously few organisms are present in the blood, joints, heart, etc.

EXPERIMENTS

The experimental lesions to be reported were produced by injecting streptococci in many places into the subcutaneous tissues of rabbits. The organism used was a strain isolated before death from the blood of a patient having acute rheumatic fever. This strain had been kept on blood agar medium with frequent transfers over a period of eight years. The amount of sediment of organisms which would settle at the bottom of a test tube of a broth culture at forty-eight hours' incubation at 37 C. was used as a unit. The broth was poured off, and the sediment was made up with physiologic solution of sodium chloride to 10 cc. One-tenth cubic centimeter of the suspension or $\frac{1}{100}$ of the sediment (the larger dose) was injected into each of ten places in the subcutaneous tissues in the back of each animal on the right side, and $\frac{1}{1000}$ of the suspension (the smaller dose) was injected in a similar manner on the left side. By a series of previous experiments with increasing amounts, the dose of $\frac{1}{100}$ of the sediment was found to be the minimum amount which would produce subcutaneous nodules in normal animals with any degree of frequency, and it was found that with the dose of $\frac{1}{1000}$ of the sediment nodules were seldom produced. The animals were killed five days after the multiple injections were made. From previous experiments, it had been found that five days after the multiple injections was the optimum time for the development of subcutaneous nodules. The nodules, if present, were studied by gross and microscopic examination.

The experiments were performed with the following three groups of animals: (1) animals that had not had injections (normal animals),

(2) animals into which streptococci had been injected intravenously (immune animals), (3) animals into which in one area agar at 45 C, heavily seeded with streptococci, had been injected subcutaneously (allergic or hypersensitive animals) By this last method, Swift found it possible to keep his animals in the hypersensitive state Before injections were made into any of the animals, blood was taken from the heart and tested for agglutinins in dilutions of 1 50 and upward Agglutinins were detected in none

Normal Animals (Group 1)—In these experiments, the animals of the first group were used as controls After the blood of a normal animal had been tested for agglutinins and found to be negative, injections were made into the subcutaneous tissues of the back in many places with the larger dose in the right side and the smaller dose in the left side, as described Five days later, the rabbits were killed

TABLE 1—Results of Subcutaneous Injection of Streptococci into Normal Animals

Rabbit	Nodules on Right Side	Nodules on Left Side	Agglutination	
			At Time of Multiple Injections	When Animals Were Killed
1	3 small	0	0	200
2	1 small	0	0	200
3	2 small	0	0	200
4	1 small	0	0	200
5	2 small	0	0	0
6	3 small	3 very small	0	0
7	2 medium	0	0	0
8	0	0	0	200
9	0	0	0	0
10	0	0	0	0

and the nodules were examined The blood was tested again for agglutinins The experiments of this group are explained in table 1

It is observed, by referring to table 1, that the inflammatory reaction in these ten normal animals was slight At least ten injections were made on each side Nodules were present with the larger doses in seven of the ten animals, but the number of nodules compared with the number of injections was small All of these nodules were small, except in one case in which the two nodules were of medium size In only one of the ten animals were there any nodules on the side into which the smaller dose had been injected These nodules were very small

By microscopic examination, the reaction in the smaller nodules was seen to be polyblastic There were regular and irregular mononuclear and multinucleated cells, plasma cells, eosinophils, lymphocytes and a few polymorphonuclear leukocytes In the centers of the few larger nodules, abscess formation was present, but a considerable degree of polyblastic reaction was always present in the periphery of these nodules

Agglutinins were not present in any of the animals in this group at the time of the multiple injections. Five days after the multiple injections, five of the ten rabbits showed agglutinins in dilutions as high as 1:200. A titer of 1:200 is low when compared with the titer in the animals into which streptococci had been injected intravenously before the multiple injections. There was no apparent relation between the presence of these agglutinins and the number, size or character of the nodules in the normal animals.

TABLE 2—Results of Subcutaneous Injection of Streptococci into Immune Animals

Rabbit	Number of Days Between Initial Dose and Multiple Injections	Nodules on Right Side	Nodules on Left Side	Agglutination	
				At Time of Multiple Injections	When Animals Were Killed
A	1	1 small	0	0	400
	2	1 small	0	0	400
	3	0	0	0	400
	4	0	0	0	400
	5	0	0	100	6,400
	6	0	0	100	6,400
	7	0	0	100	6,400
	8	0	0	100	6,400
	9	0	0	200	6,400
	10	0	0	200	6,400
	11	0	0	200	6,400
	12	2 small, firm	0	200	6,400
B	1	0	0	6,400	6,400
	2	4 medium	2 small	6,400	6,400
	3	6 medium	0	6,400	6,400
	4	2 medium	0	6,400	6,400
	5	3 medium	0	6,400	6,400
	6	3 small	0	6,400	6,400
	7	6 large	5 small	6,400	6,400
	8	5 medium	0	6,400	6,400
	9	5 medium	4 small, firm	6,400	6,400
	10	6 medium	3 small, firm	6,400	6,400
	11	8 medium	3 small, firm	6,400	6,400

Immune Animals (Group 2)—The second group consisted of thirty-one animals in which immunity, indicated by the presence of agglutinins, had been produced by an intravenous injection of streptococci. Multiple injections with $\frac{1}{100}$ and $\frac{1}{1000}$ of the sediment of a broth tube, as in group 1, were made subcutaneously into the tissues of the backs of the different animals at intervals of one, two, three, four, five, six, seven, eight, ten and twelve days (table 2). Eight other animals were highly immunized by being given four intravenous injections at intervals of five days. Seven days after the last intravenous injection, the multiple subcutaneous injections were given (table 3). The purpose of the experiments with the immune animals was to determine whether the progress of the cellular reaction at the points of the secondary multiple subcutaneous injections was increased as a result of a hypersensitive

condition occurring early in the development of a general immunity, as suggested by Zinsser,⁶ whether the reaction was retarded from acquired resistance, or whether a hypersensitive state developed near the twelve-day period following the primary intravenous immunizing dose. The results of these experiments are given in tables 2 and 3.

By table 2 it is seen that little reaction occurred, as indicated by the frequency, size and character of the subcutaneous nodules in the animals in the first half of the experiment or in the twelve animals which had received the multiple subcutaneous injections in from one to five days after the primary intravenous immunizing dose (table 2A). Nodules were present in three of these twelve animals. Only 4 nodules were seen of a possible 240. These four nodules were all on the right side, into which the larger doses were injected. The nodules were small

TABLE 3—Results of Subcutaneous Injection of Streptococci into Hyperimmune* Animals

Rabbit	Nodules on Right Side	Nodules on Left Side	Agglutination	
			At Time of Multiple Injections	When Animals Were Killed
1	1 small	0	64,000—	64,000—
2	2 small, firm	2 small, firm	64,000+	64,000+
3	0	0	64,000—	64,000—
4	0	0	256,000	300,000
5	0	0	256,000	300,000
6	2 small, firm	0	256,000	300,000
7	2 small, firm	0	256,000	300,000
8	0	0	26,000	00,000

* Animals were rendered hyperimmune by four intravenous injections of streptococci at intervals of five days.

and firm and by gross examination did not appear to be abscesses. It was evident that these twelve rabbits showed no degree of hypersensitivity, and there was a suggestion that they had some degree of resistance since the number and the size of the nodules were less than those found in normal animals.

Marked reaction took place in the eleven animals in the second half of group 2, the immune animals that had had the multiple subcutaneous injections in from six to twelve days after the primary intravenous inoculation (table 2B). The nodules were more frequent, were larger and sometimes occurred on the side into which the smaller doses were injected. In all of these eleven animals except one nodules were produced from the larger injections and in five from the smaller injections. They ranged in number from two to eight on the right side and from three to five on the left side. Into each side ten injections had been made.

6 Zinsser, H. and Yu, H. Bacteriology of Rheumatic Fever and Allergic Hypothesis, Arch. Int. Med. 42: 301 (Aug.) 1928.

The microscopic reaction differed in no way qualitatively from that found in the normal animals. No peculiarity in the reaction was observed.

Two factors may be thought of as the cause of this difference in the quantitative reaction in the two divisions in group 2: (1) the interval of time between the multiple subcutaneous injections and the primary immunizing inoculation, and (2) the degree of concentration of the immune bodies in the blood of the animals. It will be observed that in the twelve animals with little reaction (table 2A) the interval of time between the immunizing dose and the multiple subcutaneous injections was from one to five days, while in the eleven animals with the marked reaction (table 2B) the interval was from six to twelve days. The increased reaction in the second division might have been due to some degree of allergy, since allergic reactions are likely to occur in from six to fifteen days after an initial injection. It may be noticed that the degree of concentration of antibodies in the blood of the animals with little reaction was relatively low. It was never above 1:200 at the time of the multiple subcutaneous injections, and in four of the twelve animals no agglutinins were present at this time. The agglutinins at the time when the animals were killed, however, were high, 1:6,400+, in all, except in those in which the subcutaneous injections were made one day after the initial dose. In all the animals with marked subcutaneous nodules, the agglutinating titer was high, 1:6,400+, both at the time of the multiple subcutaneous injections and when the animals were killed.

Experiments were performed with the highly immunized animals in an attempt to determine whether the high antibody content of the serum rather than a hypersensitiveness was responsible for the greater frequency and larger size of the nodules. Only four of the eight animals highly immunized showed subcutaneous nodules (table 3). There was but one small nodule in the first animal, and this nodule was on the side into which the larger dose was injected. The second animal had two of a possible twenty nodules on each side. These four nodules were small and rather firm. The third, fourth, fifth and eighth animals had no nodules. The sixth and seventh animals each had two small firm nodules on the side into which the larger dose had been injected. In the eight animals there were 9 nodules of a possible 160. The microscopic structure of these nodules in the hyperimmunized animals was similar to that found in the small nodules in all the other groups.

It is to be observed that the agglutinating titer was high, 1:64,000 and 1:300,000. The experiments with these highly immunized animals suggested that the frequency and the size of the subcutaneous nodules were not increased by a high antibody content and that, when there was an increase in the number and size of the subcutaneous nodules

in animals which previously had had intravenous injections, this increase was due to a hypersensitive, or allergic, reaction, reaching its maximum intensity in from ten to twelve days after the primary intravenous injections, as it did in animals made hypersensitive from agar and streptococci

Hypersensitive Animals (Group 3)—Five cubic centimeters of melted agar at 45 C heavily seeded with streptococci, was injected subcutaneously into one area in each of the twelve animals of the third group. An abscess regularly developed at the point of inoculation. In from twelve to fifteen days multiple subcutaneous injections were made into the back and sides of each animal with the larger and smaller doses of streptococci, $\frac{1}{100}$ of the sediment of a broth tube in each injection on the right and $\frac{1}{1000}$ on the left, as in groups 1 and 2. An interval of from twelve to fifteen days between the local injection and the secondary multiple injections was found by previous experiments to be the optimum for producing the best subcutaneous nodules.

The purpose of this experiment was to see whether the reaction following the secondary multiple subcutaneous injections was different, when a localized lesion was present, from the reaction occurring in the multiple subcutaneous nodules in normal animals and in animals immunized by intravenous injection. Swift showed by skin reactions that the allergic state depending on the localized lesion differed from the immune state which was produced by intravenous injection. This idea was held by Zinsser⁷ and was expressed by Baldwin⁸ and Krause⁹ relative to the skin test in its relation to tuberculosis. The results of the experiments with the third group of animals are explained in table 4.

The gross reaction was pronounced in this group of animals. With the larger dose all of the twelve, except one, showed subcutaneous nodules and, with the smaller dose, nodules were present in all but three. With both doses, it should be observed that, as a rule, there were numerous nodules, many of which were large (fig. 1). The larger nodules were generally abscesses, and frequently there was a large red zone of injection about the area of abscess. It was obvious that the reaction in this group was definitely more extensive than in the other two groups. The production of nodules was evidently stimulated, in the hypersensitive animals, by smaller doses than in the normal or the immune animals.

7 Zinsser, H., and Mueller, J. H. Nature of Bacterial Allergies, *J. Exper. Med.* **41** 159, 1925. Zinsser, H. On the Significance of Bacterial Allergy in Infectious Diseases, *Bull. New York Acad. Med.* **4** 351, 1928.

8 Baldwin, E. R. Studies in Immunity to Tuberculosis, *J. M. Research* **22** 189, 1910.

9 Krause, A. K. Studies in Immunity to Tuberculosis, *J. M. Research* **24** 361, 1911.

The microscopic type of reaction was both polyblastic and exudative. The exudative reaction was more pronounced than in the normal and immune animals. Abscesses were common. All the larger nodules had abscesses in the centers. Many of the abscesses were large (fig 1). The polyblastic type of reaction which was present in the smaller nodules did not differ in character from that found in the normal animals and in the animals immunized by intravenous injections of streptococci.

It should also be noticed that in only five of the twelve animals was there any agglutinating titer at the time of the secondary inoculations and in these the titer was not above 1:400. The agglutinating titer when the animals were killed was also low, never being above 1:400 and in one case it was absent entirely. It was evident that there was a decided hypersensitive state in this group of animals and that this

TABLE 4—*Results of Subcutaneous Injection of Streptococci into Hypersensitive Allergic Animals*

Rabbit	Nodules on Right Side	Nodules on Left Side	Agglutination	
			At Time of Multiple Injections	When Animals Were Killed
1	Many large	Many medium	0	0
2	Few small	0	0	200
3	0	0	0	200
4	Many small	0	0	200
5	Many large	Many small	0	200
6	Many large	Many small	0	200
7	Many large	Many small	0	200
8	Many large	Few small	200	400
9	Many large	Few small	200	400
10	Many large	Many large	400	400
11	Many large	Many large	400	400
12	Many large	Many large	400	400

hypersensitiveness was not dependent on a high humoral immunity, as indicated by the concentration of agglutinins, but depended on something in these animals which was not present or conspicuous in the first two groups. The conspicuous condition in group 3 which was absent in groups 1 and 2 was the primary abscess resulting from the injection with agar heavily seeded with streptococci. Something bound up with the abscess seemed to be responsible for the hypersensitiveness. This idea is in accord with the observations of Baldwin and Krause and the experiments of Swift and his co-workers. Just what this substance or condition is has apparently been determined by workers in immunity. It has been suggested by Zinsser and by Avery and Heidelberger¹⁰ that the protein of the organism is split up in the lesion and results in a changed antigen which stimulates the hypersensitiveness observed.

¹⁰ Avery, O. T., and Heidelberger, M. Immunologic Relationships of Cell Constituents of *Pneumococcus*, *J. Exper. Med.* **42**: 367, 1925.

COMMENT

Experimental streptococcic inflammatory lesions were studied by both gross and microscopic examination in animals under three specific conditions (normal immune and hypersensitive, or allergic). The lesions studied were produced by the injection of small doses of streptococci into the subcutaneous tissues of the backs and sides of rabbits. These multiple small injections were spoken of as the multiple secondary injections or inoculations. The same doses were used in producing the



Fig 1—Subcutaneous nodules (abscesses) in a hypersensitive animal

multiple subcutaneous lesions in all the animals in the three groups. The larger dose was $\frac{1}{100}$ of the sediment of a broth culture of streptococci, and the smaller dose was $\frac{1}{1000}$ of the sediment.

The first group of animals had not had any previous injection and showed no agglutinins for streptococci at the time of the multiple subcutaneous injections. These animals were the controls or normal animals. The second group consisted of animals which had been given an immunizing dose of streptococci intravenously. Most of these showed agglutinins in the blood at the time of killing and some at the time of

the secondary injections. The titers of the agglutinins varied according to the interval of time between the multiple subcutaneous injections and the intravenous injection. The animals of the second group were called the immune animals. The third group consisted of animals which had received one subcutaneous injection of agar at 45 C, heavily seeded with streptococci. Agglutinins in the blood of most of these animals were absent at the time of the secondary multiple subcutaneous injections and low at the time when the animals were killed. These animals were called the hypersensitive animals.

In the normal animals, few gross lesions were detected following the injection of either dilution. In the immune animals, when the subcutaneous inoculations were made before the seventh day after the immunizing inoculation, practically no lesions developed. Those animals in which the subcutaneous injections were made from the seventh to the twelfth days showed a greater frequency of lesions than did the normal animals. This greater reaction was probably due to an allergic reaction, since other animals highly immunized from several intravenous injections did not have this increased reaction. On the other hand, a retardation was shown. In the hypersensitive animals, gross lesions, often large abscesses, were practically always present with both the larger and the smaller doses. Abscesses were much more common in the hypersensitive animals than in the normal or the immune animals.

Two types of cellular reaction were noted in the nodules in all the experiments reported in this paper: (1) the exudative reaction, generally with necrosis and abscess formation, and (2) the polyblastic reaction. The cells chiefly found in the exudative reaction were polymorphonuclear leukocytes. In the polyblastic type of reaction, various cell types were seen, but the scarcity or absence of polymorphonuclear leukocytes was conspicuous. In the polyblastic lesions there were regular and irregular mononuclear and multinucleated cells with basophilic cytoplasm, plasma cells, eosinophils and lymphocytes. In some nodules, the more or less regularly shaped cells predominated. They gave the appearance of having wandered in (fig 2). In other nodules, the cells were mainly irregular or elongated in shape and suggested that they might have developed from the existing cells in the region of the nodule (fig 3).

The polyblastic type of microscopic cellular reaction was found in all three groups. No difference could be detected in the character of the reaction in the nodules. Polyblastic inflammation free from abscesses was less common in the hypersensitive animals, since the nodules were larger and the larger nodules regularly became abscesses.

It appears evident that the polyblastic type of reaction, which is characteristic of the lesions found in patients with acute rheumatic fever, does not depend primarily on a hypersensitive stage, when produced experimentally in animals. If doses sufficiently large are given,



Fig 2—Microscopic structure of a subcutaneous nodule with polyblastic inflammation, $\times 450$ The cells appear to have wandered in

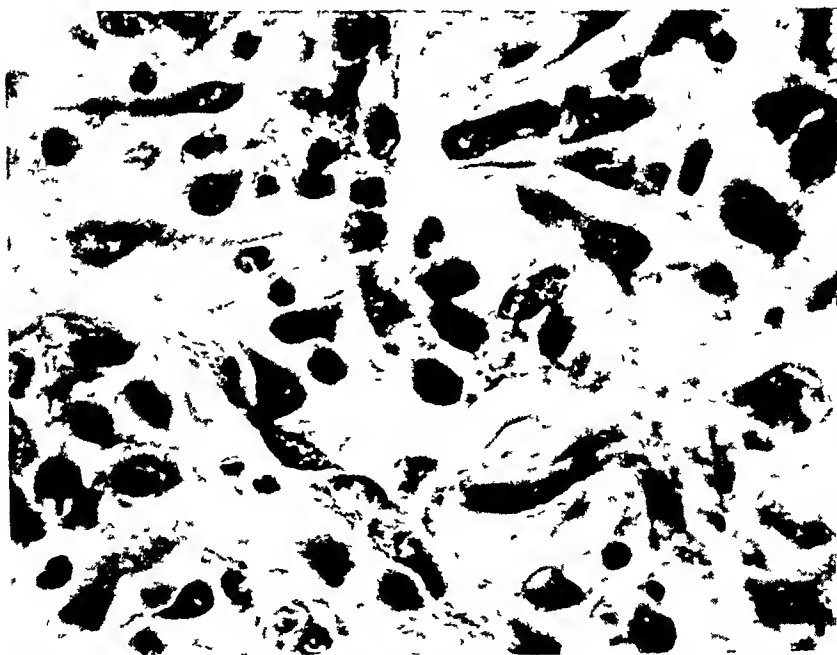


Fig 3—Microscopic structure of a subcutaneous nodule with polyblastic inflammation, $\times 450$ The polyblasts appear to have developed from existing cells in the area of the nodule

this reaction may be produced in both normal and immune animals, as well as in hypersensitive animals

It is evident, however, that doses which in normal or immune animals have no noticeable effect or produce only small, firm polyblastic nodules, will, in hypersensitive animals, stimulate the production of definite nodules, many of which are extensive enough to be abscesses. The relationship between allergy and the polyblastic type of reaction appears to be, as suggested by Maximow, a quantitative one. This quantitative relationship may help to explain the pathogenesis of human rheumatic lesion in many cases. Since streptococci have not been found in large numbers in the blood and joints of patients having acute rheumatic fever, it has been difficult to understand the extensive lesions, but when it is taken into account that very small doses of streptococci produce extensive reactions in hypersensitive animals and that high percentages of patients having acute rheumatic fever are hypersensitive to streptococci, the pathogenesis of the human lesions can more readily be understood.

SUMMARY

Experimental subcutaneous nodules with a polyblastic type of inflammation can be produced in normal, immune and allergic (hypersensitive) animals by regulating the dose of the injection.

Such nodules can be produced with much smaller doses in the hypersensitive animals.

General immunity, as indicated by a high agglutinating titer, tends to retard the development of subcutaneous nodules, except in cases in which the subcutaneous injections are made in from seven to twelve days after the primary immunizing inoculations. In these cases, the increased nodular production is probably due to allergy.

The larger nodules in all cases, as a rule, are abscesses, hence, the greater frequency of abscesses in the hypersensitive animals.

The relationship between allergy and the pathogenesis of experimental rheumatoid subcutaneous nodules appears to be quantitative only.

When these experimental results and the frequency of the hypersensitive state in patients with acute rheumatic fever are considered, it becomes less difficult to understand the pathogenesis of human rheumatic lesions.

CHRONIC PASSIVE CONGESTION OF THE LIVER

AN EXPERIMENTAL STUDY

H M ZIMMERMAN,¹ M D

AND

JOHN A HILLSMAN, M D

NEW HAVEN, CONN

The association between cardiac decompensation and hepatic cirrhosis has long been recognized. Kiernan's description, in 1833, of the "nutmeg liver" as the "second stage of congestion," has been followed by considerable controversy as to the etiologic factor or factors in the production of this pathologic picture. At the present time, it is believed by some that the central cirrhosis of the liver in cardiac decompensation is the result of necrosis of the liver cells around the central veins with a consequent shrinkage and condensation of the fibrous tissue normally present in that locality. Others believe that the destruction of the hepatic cells is followed not by condensation of the fibrous tissue normally present, but by an actual proliferation of this tissue to produce the cirrhosis. Still others believe that not only does the factor of mechanical pressure play a part in the production of this picture, but a toxic agent in addition, is necessary to cause a stimulation of connective tissue proliferation.

Unfortunately, these various opinions have been formed through the study of human autopsy material and the little investigation that has been done on experimental animals has in the majority of instances been unsatisfactory.

Such observation of this condition has not been convincing as regards etiology, first, because it is impossible to rule out the toxic agent as a factor in the production of cirrhosis, secondly because the lesions studied are most often, if not exclusively, the late rather than the early ones. Lambert and Allison¹ gave an excellent anatomic description of the changes in the liver usually associated with this condition and believed that the resultant central fibrosis is only an apparent increase in the amount of fibrous tissue due to condensation. Mallory² held the

* Submitted for publication, Jan 10, 1930

¹ From the Departments of Pathology and Surgery, Yale University School of Medicine

1 Lambert, R A, and Allison, B R. Types of Lesion in Chronic Passive Congestion of the Liver, *Bull Johns Hopkins Hosp* **27** 350, 1916

2 Mallory, F B. Chronic Passive Congestion of the Liver, *J M Research* **24** 455, 1911

view that a toxic agent is a necessary adjunct in the production of the central fibrosis. The experimental work of Bolton³ is by far the most convincing. This observer produced experimentally a partial to complete obstruction of the inferior vena cava between the liver and the heart in animals and observed the central necrosis and condensation of fibrous tissue. He did not find active proliferation of the connective tissue cells.

The problem that presented itself to us was the production of a simple obstruction to the outflow of blood from the liver in dogs without the presence of any demonstrable toxic factor and the study of the mechanism of the production of changes in the liver structure over a long period of time.

EXPERIMENTAL TECHNIC

In general, the procedure used was to constrict by ligature the thoracic portion of the inferior vena cava to about one half of its normal diameter, and then, at stated intervals, to remove, through abdominal incisions, portions of different lobes of the liver for microscopic study. In all, sixteen dogs were used in the experiments, and several dogs had as many as four abdominal operations for the removal of portions of the liver.

In particular, the procedure was as follows. The dogs were placed under ether anesthesia by the ordinary "drop method." A "mushroom" catheter was then inserted into the trachea, the cap of this catheter entirely occluding the lumen and giving complete control of respiration for purposes of positive pressure. To the end of the catheter was attached a glass T-tube through which passed the air-ether mixture at a pressure indicated with a mercury manometer placed in the circuit. By alternately closing and opening the free end of the T-tube, both the rate of respiration and the depth could be accurately controlled. The operative procedure was to make an incision following the curve of the right sixth rib anteriorly. About 4 inches (10.16 cm.) of this rib, as close to the midline as possible, was then resected subperiosteally. The pleural cavity was entered and the right lung packed upward, exposing the inferior vena cava. The right phrenic nerve was then dissected free of this vessel for a distance of about 1 inch (2.5 cm.) and an aluminum band placed around the vena cava as close to the pericardial sac as possible with the apparatus devised by Halsted. The metal band was compressed digitally until the desired constriction of the vena cava was achieved. The parietal pleura and the intercostal muscles were sewed with a continuous catgut suture, the lung being freely expanded as the last stitch was taken. Interrupted sutures were used in the superficial muscles and on the skin. All the experiments that we shall report were made on animals that at no time showed evidence of infection.

RESULTS

Among the first of the problems that presented itself for solution was the extent of ligation of the inferior vena cava requisite for the production of chronic passive congestion. The venae cavae of three animals were ligated to produce a narrowing of the lumen to less than

³ Bolton C. The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, *J Path & Bact* **19** 258, 1914-1915

one-quarter the normal size, and in each instance the animal soon died dog 1 at the end of eleven hours, dog 2 at the end of thirty hours and dog 3 at the end of sixty hours. From the time the animals recovered from the anesthesia until death, they vomited frequently and retched continuously. There were no signs of jaundice. The remainder had the vena cava ligated to about one-half its normal diameter and lived until killed.

Eleven Hours After Partial Ligation of the Inferior Vena Cava (About 90 Per Cent Occlusion)—About 100 cc of blood-tinged fluid was present in the left pleural cavity and a somewhat less amount in the right. Petechial hemorrhages were present beneath the pleurae of both lungs and beneath the epicardium. The lungs were fully expanded. Approximately 1,000 cc of bloody fluid was present in the peritoneal cavity. The stomach and intestines were markedly distended with gas. The liver was small, tense, deep red and congested. On section, there were present throughout dark red central areas surrounded by narrow borders of paler red columns of liver cells. None of the other abdominal viscera were congested.

Microscopic examination revealed diffuse necrosis of the whole liver. The columns of liver cells in the areas about the central veins were replaced by irregular pools of red blood cells many of which were laked. The periphery of the hepatic lobules still showed the columnar and sinusoidal arrangement but the liver cells were all devoid of nuclei. Indeed field after field was viewed without one revealing a single nucleus and this extensive necrosis involved the Kupffer cells and the perilobular connective tissue cells, as well as the hepatic cells.

Thirty Hours After Ligation of the Vena Cava (90 Per cent Occlusion)—About 50 cc of a serosanguineous fluid was present in each pleural cavity and more than a liter of clear amber fluid in the peritoneal cavity. The aluminum band was in place around the vena cava and constricted this vessel to one-third its former diameter. The liver was tense and markedly congested.

Beneath Glisson's capsule were irregularly distributed small foci of widely dilated liver sinusoids which were engorged with well preserved red blood cells. Around the central veins there was necrosis of the liver cells, as well as of the endothelial cells lining the liver sinusoids, but the peripheries of the lobules showed no evidence of injury. The perilobular spaces were free from cellular infiltrations.

Sixty Hours After Ligation of the Vena Cava (90 Per Cent Occlusion)—In this animal, as in dog 1, vomiting and retching were prominent features following the operation. At necropsy, the lungs were found fully expanded, but they were congested. About 200 cc of blood-tinged fluid was present in the right pleural cavity, and about

50 cc in the left. The Halsted band around the inferior vena cava constricted this vessel about 90 per cent. In the abdominal cavity was present about 2,000 cc of cloudy, serosanguineous fluid in which floated large flakes of gray fibrin. The liver was tense and deep red, and the liver lobulations were distinct even on external view. On section the surfaces bled readily.

Again, the subcapsular liver sinusoids were engorged with well preserved red blood cells. There was hemorrhage into the parenchyma of the liver, most marked around the central veins. In these areas, the liver cells and the Kupffer cells, as well as the walls of the central veins, had entirely disappeared. Pools of blood of irregular outline occupied fully two thirds of each hepatic lobule and, lying in a central position in the lobule, replaced the normal architecture. These zones of hemorrhage were fringed by compressed liver cells which stained well and showed no nuclear disintegration. Already there could be seen delicate, spindle-shaped fibroblasts growing out into the central zones of hemorrhage. Mitotic figures or cellular exudates of any kind were absent. Occasionally, a sublobular vein was found the wall of which could just be distinguished, lying in a zone of necrosis.

Six Days After Ligation of the Vena Cava (50 Per Cent Occlusion)—Ascites was slow in onset, and at the time the animal was killed (with ether) no fluid was found in the pleural cavities, and only about 1,000 cc of faintly blood-tinged fluid was present in the abdomen. This dog showed none of the vomiting and retching which the previous dogs displayed to so marked a degree.

As in the other animals, the liver was markedly congested and showed dark red central zones bounded by narrow borders of much paler tissue.

By far the best preserved liver cells were those which formed the columns immediately beneath the liver capsule, and that was in spite of the compression to which they were subjected by the greatly distended liver sinusoids. Several features were now present in addition to those already enumerated in the previous experiments. Mallory connective tissue stains showed a thickening by blue-staining connective tissue fibers of the walls of the central veins. In some places, this connective tissue proliferation had led to acini-like formation around these veins, large spaces resembling blood vessels lay here filled with the homogeneous pink-staining material of coagulated blood serum. Numerous mitotic figures were present in liver cells that formed the edges of the central zones of necrosis.

Nineteen Days After Ligation of the Vena Cava (50 Per cent Occlusion)—Nineteen days after the partial ligation of the inferior vena

cava, dog 9 was anesthetized with ether and a laparotomy performed. The abdomen contained over 3,000 cc of clear yellow fluid. The liver was large and mottled red and yellow, resembling closely the "nutmeg liver." The surface was finely but irregularly granular, each granulation measuring no more than 2 mm in diameter. A wedge-shaped piece of liver from the left lobe was removed with the electric cautery for microscopic examination.

The process of central fibrosis was gradually increasing in extent. Spindle-shaped fibroblasts were present in the center of each hepatic lobule and completely replaced liver cells, as well as endothelial cells (Necrotic liver cells were still seen bordering these areas of fibrosis). Zones of newly formed but greatly dilated vessels were seen around each central vein in the loose connective tissue.

Sixty-One Days After Ligation (50 Per Cent Occlusion)—Once more dog 9 was anesthetized with ether and a laparotomy performed. The abdomen was free from excess fluid. The collateral venous circulation in the anterior abdominal and thoracic walls was not established to any marked degree. The retroperitoneal veins were small. The scarring of the liver noted at the end of nineteen days had progressed and now the external surfaces were coarsely and irregularly granular. Again, a wedge-shaped piece this time from the right lobe, was removed with the electric cautery.

From the histologic picture, it was at once apparent that the fibrosing process had progressed in the interval of twenty-two days. The central fibrotic areas now involved fully two thirds of each hepatic lobule. Narrow bands of liver cells containing large fat granules were present at the periphery of each lobule. The connective tissue was more dense in structure and stained a brilliant blue with the aniline blue stain. There was a marked increase in the size of the vascular channels in this connective tissue, many of them being several times larger than the central veins themselves. Occasionally, they were filled with red blood cells, but more often they contained homogeneous coagulated material and then they appeared as tortuous cystlike formations. Often, strands of connective tissue from the central areas extended to the capsular surface and appeared to draw the capsule in, producing indentations which in the gross appeared as the depressions between the granular nodules. The liver sinusoids beneath the capsule were dilated to such a degree as to be several times the diameter of the largest central veins. There was no evidence of a cellular reaction of the exudative type anywhere in the many sections studied.

Sixty-Three Days After Ligation (50 Per Cent Occlusion)—A laparotomy was performed on dog 14 following a partial ligation of the



Fig 1—Drawing of an area about a central vein, magnified 93 times to show the scar tissue and the pseudocyst formations

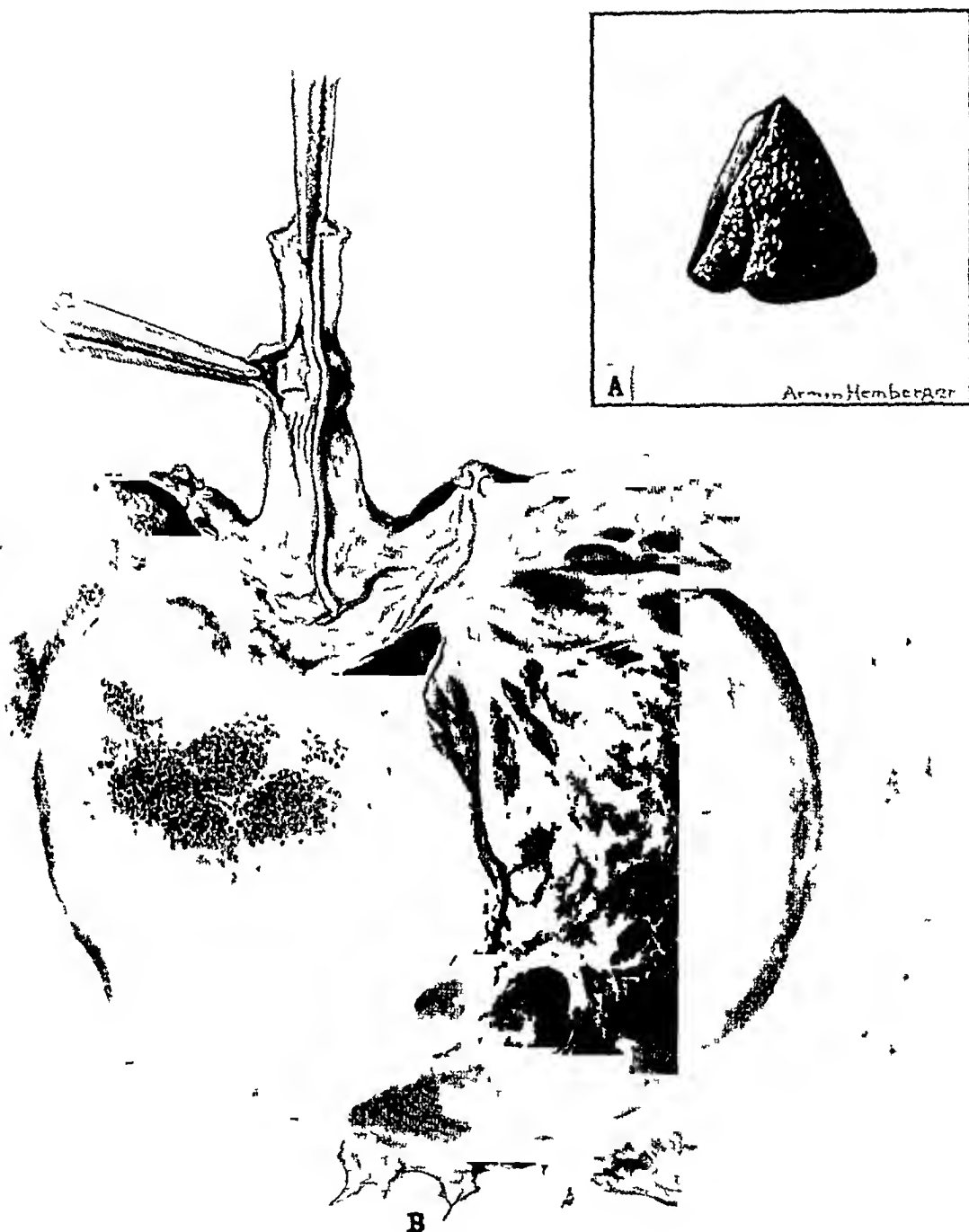


Fig 2—*A*, wedge-shaped piece of liver removed sixty-three days after the partial ligation of the inferior vena cava. Note the finely granular surface. *B*, liver of dog the vena cava of which was partially ligated 137 days previously. Note the metal band around the inferior vena cava and the scarring of the liver.

inferior vena cava sixty-three days previously. The abdominal cavity contained a little over 3,000 cc of straw-colored fluid stained with blood pigment. The external surfaces of the liver were moderately granular (fig 1), these granules being either deep purple or light red. Those lighter in color were of a much softer consistency. The liver cut with increased resistance. A portion of the left lobe was removed with the electric cautery.

In general, the histologic picture (fig 1) was similar to that described for the forty-one-day experiment, with the following additions. The subcapsular venous sinuses were dilated to a degree similar to that seen in the areas around the central veins, and there was also an apparent though slight increase in the connective tissue in this location, but whereas in the central areas the fibrosis was the result of an active proliferation of connective tissue, that in the subcapsular areas was at best in great part due to a shrinkage or disappearance of the hepatic cells by compression, with a consequent predominance of connective tissue.

Eighty-Five Days After Ligation (50 Per Cent Occlusion)—Twenty-two days after the last laparotomy, dog 14 was again explored, and it was found that over 2,000 cc of slightly blood-tinged fluid had reaccumulated in the peritoneal cavity. The liver surfaces were mottled dark red and pale bright red, and they were also granular. A portion of the right lobe of the liver was removed by knife, and then the bleeding surfaces were cauterized with an electric cautery.

A rather surprising microscopic observation was the numerous hemorrhages into the parenchyma of the liver occupying subcapsular and midzonal positions. As the centers of the hepatic lobules were occupied by dense scar tissue and pseudocysts, the hemorrhagic foci lay on the periphery of these scarred zones. The walls of the central veins were increased in thickness three or four times.

One Hundred and Thirty-Seven Days After Ligation (50 Per Cent Occlusion)—Dog 14 was killed with ether at the end of 137 days after the ligation of the inferior vena cava. This time, the abdomen was free from excess fluid. To a small area on the superior surface of the liver (fig 2) were adherent dense fibrous tags which bound it to the operative scars in the anterior abdominal wall. All surfaces of the liver were mottled with alternating dark red and bright red patches which varied in size from 2 mm to 1.5 cm in diameter. Coarse and fine granulations covered all the surfaces of the liver. On section, the bright red mottlings appeared to be beneath the capsule for only short distances. The inferior vena cava was constricted about 50 per cent by the metal band that lay embedded in newly formed connective tissue. There was no free fluid in either pleural cavity.

The liver capsule was not thickened. Beneath it could be seen dilated venous sinusoids engorged with red blood cells. The parenchymal structure was maintained here, but the columns of liver cells were compressed. Dense bands of connective tissue followed sublobular veins to the capsule and drew it in with the resultant formation of the granulations noted grossly. The process apparently had ceased to be progressive as no hemorrhage, necrosis or cellular division was present.

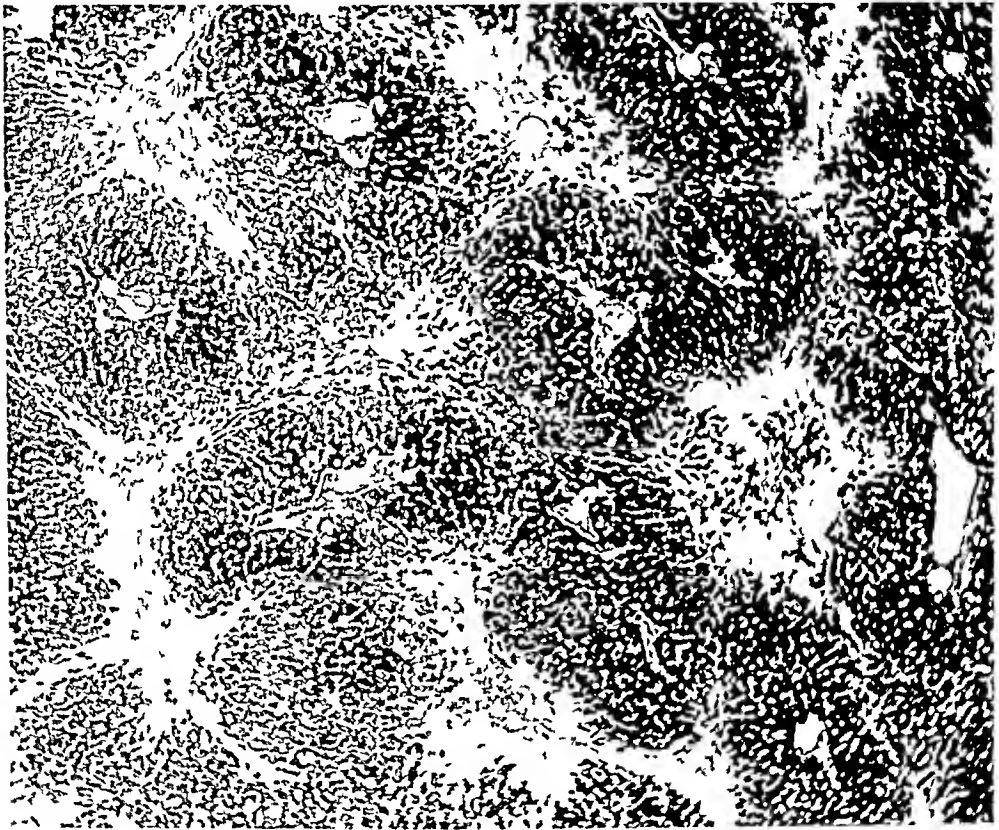


Fig. 3—Photomicrograph showing the extensive scarring in areas about the central veins, which produces a false lobulation of the liver. This condition occurred in the liver of a dog the inferior vena cava of which was partially ligated 216 days previously. Hematoxylin and eosin stain, $\times 60$.

Two Hundred and Sixteen Days After Ligation (50 Per Cent Occlusion)—Dog 15 was killed with ether 216 days after the ligation was performed. Both pleural cavities and the abdomen were free from excess fluid. The metal band constricted the inferior vena cava about 50 per cent. The external surfaces of the liver were coarsely nodular and looked not unlike those in the 137-day experiment. In the hope of determining the relationship between the pseudocysts and the central veins a mixture of barium sulphate was injected into the liver through the inferior vena cava at a pressure of 100 mm. of mercury, and on

microscopic examination this mixture was seen to fill both the central veins and the pseudocysts—a fact which proved their direct communication

Closer examination showed dense scar tissue in the areas about the central veins, often extending from one lobule into another and producing lobulations in the liver which had in their centers the periportal zones surrounded by normal liver cells (figs 3 and 4) The picture

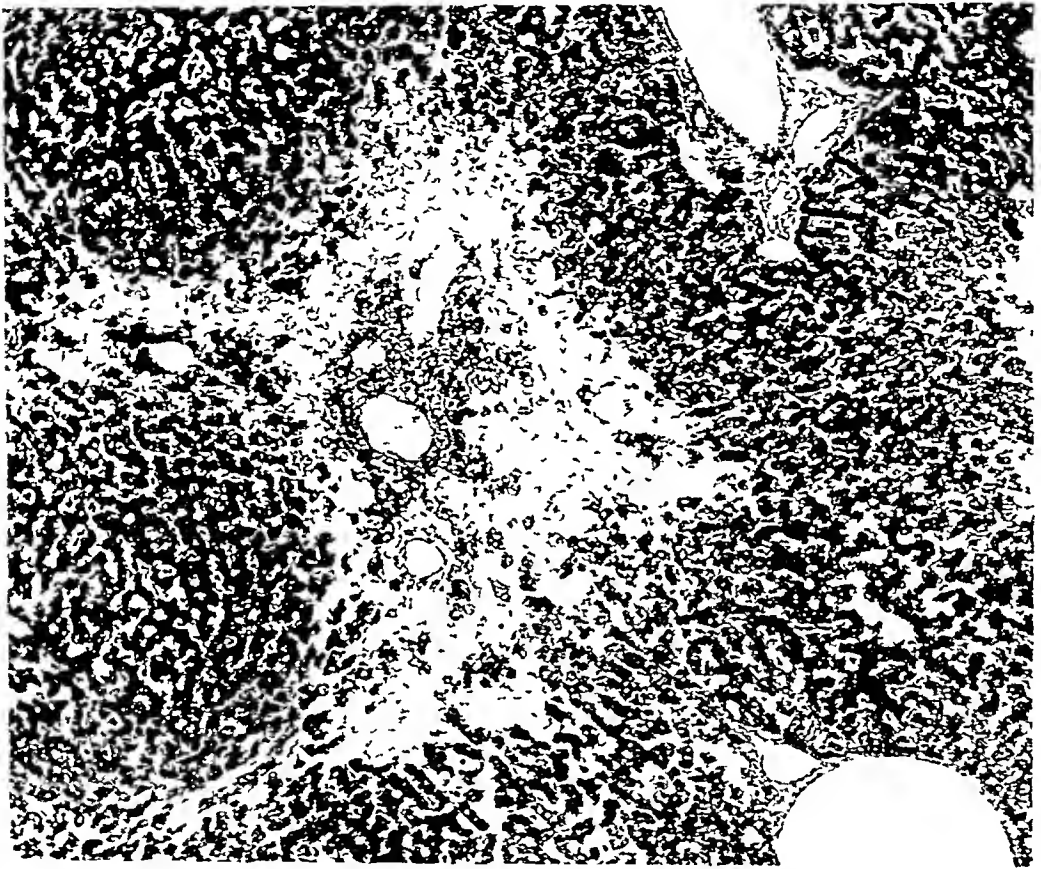


Fig 4—More detailed view of the scar tissue in the area about a central vein from the same liver as that shown in figure 3 Hematoxylin and eosin stain, $\times 225$

was similar to that seen in periportal cirrhosis or fibrosis, except that the fibrous tissue in this condition lay in a different part of the liver lobule

COMMENT

It is important to consider how far these experiments parallel the condition of chronic passive congestion so often seen at the bedside If it is at all permissible to compare lesions produced in experiments on animals with those found in man then we may argue that the obstruction to the inferior vena cava is effective in producing consequences in

the dog that a failure of the right side of the heart produces in man. If the obstruction is of such a degree only as to produce gradual congestive phenomena, then these experimental conditions approach all the more closely those existing in heart failure. In thirteen of the sixteen animals of these experiments, the obstruction was relatively slight (about 50 per cent), and the resultant ascites was gradual in onset. Also the lesions found in the livers of these animals never involved more than the immediate pericentral areas. In three of the sixteen dogs in whom the obstruction was much greater (about 90 per cent), all the signs of congestive failure were almost immediate in onset and the hepatic necrosis involved nearly all of the hepatic lobule throughout the liver. It is, perhaps, necessary to point out that even in these three animals there was no question of infarction of the liver, if by that term we mean necrosis resulting from the interference with the blood supply to an organ or a part of one. And yet it is readily admitted that the rapid course of the condition in these animals does not parallel that of persons dying from congestive heart failure. It must be pointed out also that in all our experiments the lesions were steadily progressive even when gradual and did not show the periods of apparent arrest or improvement which are so often observed clinically in persons with congestive heart failure.

It seems safe to assert that the lesion produced in these experiments was the result of a simple mechanical interference with the venous return from the liver, and that a toxin particularly one liberated in the course of an infectious process, had no part in the production of this lesion.

SUMMARY

Necrosis of the liver follows simple mechanical obstruction to the outflow of blood, the extent of the necrosis being proportional to the amount of obstruction. The necrosis can involve the whole liver eleven hours after the ligation of the inferior vena cava.

Ascites is early associated with necrosis of the liver, which is consequent to the obstruction of the inferior vena cava.

As early as six days after the partial ligation of the inferior vena cava there is evidence in the liver of repair, as manifested by the numerous mitotic figures and the increase in the connective tissue in the areas around the central veins.

Nineteen days after partial ligation of the inferior vena cava the liver shows grossly the picture of chronic passive congestion. Active proliferation of connective tissue is seen around the central veins.

In forty-one days there are marked distention of the subcapsular venous sinusoids and marked fibrosis of the areas about the central veins with large vascular spaces newly formed in this scar tissue.

The cystlike formations in the connective tissue around the central veins are branches of these vessels

The fibrosis ceases to increase in extent after eighty-five days and is essentially of the same extent 216 days after the ligation of the inferior vena cava

Central fibrosis of the liver can result without infection being present, and is due to an active proliferation of connective tissue

MECONIUM PERITONITIS FROM SPONTANEOUS PERFORATION OF THE ILEUM IN UTERO*

W SCLAIR BOIKAN, M D

CHICAGO

The pathology of the fetus is still a relatively new field. The anomalies and maldevelopments have been thoroughly investigated, but from the point of view of primary developmental aberrations. There has developed recently, however, a new point of view emphasizing that not all fetal anomalies are due to developmental disturbances and that not all fetal diseases are of maternal origin. It is gradually becoming recognized that the same factors causing disease in extra-uterine life are operative also in utero. Thus, intestinal obstruction, perforation of the intestines and peritonitis are equally explained by incarceration in hernias, strangulation by bands, intussusception, etc. The study of the pathology of the fetus has cast much light on fetal physiology and vice versa. Though a considerable literature has accumulated relative to the question of fetal peritonitis many problems still remain unsolved, and further observations casting some light on the problem warrant publication. For this reason I have thought it worth while to report a case of meconium peritonitis which I have had the opportunity to study and to review the literature with reference to this subject especially as the conditions present at the site of the perforation in the intestine permit an explanation not as yet offered.

Meconium peritonitis is a pathologic entity which is to be clearly differentiated from the acute bacterial peritonitis of the new-born occurring as a complication of infections of the cord, septicemia of maternal origin, syphilis (Baumgarten¹) or similar conditions. By meconium peritonitis is meant a nonbacterial foreign body and chemical peritonitis occurring during intra-uterine life as the result of abnormal communication between the bowel contents and the peritoneal cavity. As already emphasized by Gierke,² the term meconium peritonitis is only applicable to those cases in which there is demonstrable within the peritoneum, meconium, calcified meconium mucous droplets,

* Submitted for publication, Feb 27, 1930

From the Pathological Laboratories of the Cook County Hospital

1 Baumgarten, cited by Peiser, A. Die fetale Peritonitis, eine klinische Studie, Beitr z klin Chir **60** 168, 1908

2 Von Gierke, E. Bauchfell, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol 4, pt 1, p 1069

foreign body giant cells, cells from the source of perforation, fibrinous or fibrous adhesions and, rarely, lanugo hair

In the comment on the etiology it will be seen that although the conditions favorable to an intestinal perforation may arise early in intra-uterine life, the actual perforation may take place during labor or shortly afterward as a result of the increased peristalsis during this time and of the mechanical forces of the labor itself. Of course, such cases are not purely of a mechanical or chemical nature, as within from three to six hours the originally sterile intestinal contents become infected and there is then superadded a bacterial etiology for the peritonitis (Escherich,³ Kendall⁴). But a comprehensive conception that attempts to explain intra-uterine rupture should also explain intrapartum and immediately postpartum bowel ruptures, especially, since the time of rupture is extremely variable. The term, meconium peritonitis, therefore, should be applied to cases resulting from fetal or intrapartum or shortly postpartum intestinal rupture.

Meconium is a sterile mixture of cast off epithelial cells, bile pigment, bile salts, cholesterol, fat, stearic acid, sebaceous material from swallowed liquor amnii, mucin and salts (Williams,⁵ Sturzenegger⁶). Bile and its constituents are formed at about the end of the third month (Zweifel,⁷ Kolliker,⁸ Prentiss and Arey⁹). Pancreatic and gastric secretions with their enzymes are added at about the fifth month, perhaps earlier (Langendorff¹⁰ and Zweifel⁷).

The existence of peristalsis within the fetus is necessary for the production of intestinal rupture. There is no direct observational evidence, but certain facts presuppose the existence of peristalsis early in fetal life. The presence of meconium in the cecum was observed by

3 Escherich, T. Die Darmbakterien der Sauglinge, 1886, cited by Peiser (footnote 1)

4 Kendall, A. I., cited by Michael, May, in Abt, I. A. Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 7, p. 31

5 Williams, J. W. Obstetrics, New York, D. Appleton & Company, 1926, p. 392

6 Sturzenegger, F. Ein Fall von Mekonium Peritonitis mit Verhalkungen in Peritoneum und Myocardium, Beitr. z. path. Anat. u. z. allg. Path. **78** 85, 1927

7 Zweifel, H. Untersuchungen über das Meconium, Arch. f. Gynak. **7** 474, 1875

8 Kolliker, A. Development of the Intestine, in Keibel and Mall. Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, p. 390

9 Prentiss and Arey. A Laboratory Manual and Textbook of Embryology, Philadelphia, W. B. Saunders Company, 1923, p. 179

10 Langendorff, cited by Landsteiner, K. Darmverschluss durch eingedicktes Meconium, Pancreatitis, Centralbl. f. allg. Path. u. path. Anat. **16** 903 (Nov. 30) 1905

Mall¹¹ in a 130 mm embryo Broman¹² believed that the progressive course of the meconium was a factor in the development of the intestines, especially of the rectum and anus. He pointed out that anomalous communications of the small intestine or the cecum which diverted the meconium were almost regularly associated with atresia of the rectum and that the bowel below an atresia formed a firmly contracted string with a pinpoint lumen. Cases of fetal intussusception, as well as of incarceration of a loop of ileum in a hole in the mesentery of the jejunum, point to an early onset of peristalsis, similarly, the presence of marked dilatation and hypertrophy of the intestine above a constriction with thinning out at the site of constriction allow the same conclusion. Meconium, therefore, as it is formed at about the third month acts as an irritant or stimulus to peristalsis, which drives the meconium down and progressively aids in the proper development of the intestine.

The earliest time of onset of meconium peritonitis cannot, of course be determined with any accuracy. Silberman¹³ placed the period in the first third of fetal life and Mackenrodt,¹⁴ among others, in the second third. In a case reported by Rudnew,¹⁵ a dead fetus of 6 months showed a membrane 2 mm thick adherent to the intestines, with calcified plaques throughout the peritoneum. The amount and the stage of organization of the meconium and the reactive exudate are of value in estimating the duration of the peritonitis. Calcification is not as valuable, since as shown by Litten,¹⁶ the latter may take place within twenty-four hours. From Rudnew's case, one may say that fetal peritonitis may commence earlier than the sixth month, and in most cases, probably in the period between the third and the sixth month.

The reactive phenomena resulting on the entrance of meconium into the peritoneal cavity are those of a chemical and foreign body peritonitis. Dense adhesions and calcified plaques are formed as end-results. The calcification of the meconium is, no doubt, due to the precipitation of the calcium of the tissue fluids and the blood by the broken down fatty constituents. There occasionally occurs not only local but also distant calcification. Sturzenegger⁶ described a case of fetal peritonitis in

11 Mall, F. P., in Keibel and Mall (footnote 8, p. 390)

12 Broman, cited by Koch, W. *Missbildungen von Verengerungen und Verschlüsse*, in Henke, F., and Lubarsch, O. (footnote 2, p. 189)

13 Silberman, O. *Ueber Bauchfellentzündung Neugeborener*, *Jahrb. f. Kinderh.* **18** 420, 1882

14 Mackenrodt, A. *Berichte aus gynäkologischen Gesellschaften und Krankenhäusern Zentralbl. f. Gynäk.* **16** 654, 1893

15 Rudnew, W. *Ueber die spontanen Darmrupturen bei Foeten und Neugeborenen*. Inaug. Dissertation, Basel, 1915

16 Litten, cited by Rudnew (footnote 15)

which the myocardium was extensively calcified. His explanation for these distant metastases is unsatisfactory. He assumed an alkalimization of the circulating blood and of the tissue fluids as a result of absorption of alkaline salts from the meconium within the peritoneum (Hofmeister¹⁷)

REPORT OF A CASE

Maternal History—The mother was a colored woman, aged 21. It was her first pregnancy. The period of gestation had been normal, and physical examination at the time of entry revealed no abnormality. The first stage of labor was of ten hours' duration, and the infant was delivered thirty minutes after full dilatation. Parturition was uneventful. The Wassermann reaction of the blood before and after labor was negative.



Fig 1—Marked thickening of the capsule of the spleen with adherent calcified meconium plaques

Infant—The infant was full term. Physical examination shortly after birth revealed a markedly distended abdomen which was tympanitic anteriorly and dull in the flanks. There was evidence of compression in both lower pulmonary lobes. There was an easily reducible left inguinal hernia.

The labia majora were slightly edematous. Catheterization of the rectum yielded a large amount of gas. The Wassermann reaction of the blood was negative. The child was fed by breast six times a day at three hour intervals, and water and protein milk were given between feedings. Within twenty-four hours,

¹⁷ Hofmeister, F. Ueber Ablagerung und Resorption von Kalksalzen in den Geweben, *Ergebn d. Physiol* 10 429, 1910

the infant began to regurgitate all food and water and became markedly cyanotic. The distention of the abdomen had increased markedly. Rales were heard in the chest. The rectum prolapsed slightly. The infant became comatose and died twenty-six hours after birth.

Postmortem Examination—The body was that of a full term, well nourished female infant. The abdomen was markedly distended. There was a left inguinal, easily reducible hernia.



Fig 2—Perforation in the lower ileum (a) with nodules about the perforation and (b) dense fibrous adhesions

The pleural surfaces were bright and glistening. The lungs were light red, the basal portions purplish. The upper lobes were crepitant, the lower lobes subcrepitant, and the cut surface purplish pink. The heart was normal.

The abdominal cavity contained about 150 cc of a brownish, cloudy fluid in which were suspended yellowish flakes. The loops of the small intestine were matted together into a solid mass about 8 cm in diameter by fine strands which broke easily. The loops were moderately distended by gas and meconium. The serosa was a light pinkish gray and covered by numerous firmly adherent, finely granular, light yellowish-gray masses. These masses were also found on the surface of the liver and spleen (fig 1). On the inferior aspect of the liver, they

reached a maximum thickness of 2 mm. On the anterior aspect of the spleen, they were as much as 25 mm in diameter. The duodenum was drawn toward the hilus of the liver and attached rather firmly to the gallbladder.

In the ileum about 60 mm above the junction with the colon on the inferior aspect and near the mesenteric attachment there was an opening in the intestinal wall, 1 mm in diameter (fig 2).

From this opening, thick, greenish material and mucus exuded on pressure. The lower part of the ileum felt rather firm and, adjacent to the opening, there was a soft, light-red nodule 2 mm in diameter.

The spleen was large, soft and friable. The pulp was a deep red and showed no structure.

The liver weighed 90 Gm and was moderately firm. The surface was smooth, except for the yellow deposits previously described. The cut surface was brownish gray; the markings were obscure.

The kidneys weighed 20 Gm, the surface was smooth and light gray-brown. On section, the medulla was deep red.

The pelvic organs were normal. The ovaries were deep red.

The brain showed no anomalies.

Microscopic Examination—Sections were made of all the organs. In addition, serial sections were made of the bowel, including transverse sections immediately above and below the site of perforation and longitudinal sections through the perforation. The sections were 5 microns thick and every fifth section was stained. Those immediately above and below and those through the perforation were taken at three section intervals. For comparison, serial sections were made of every portion of the large and small intestine of three newly born full term infants who died of cerebral injuries and presented no anomalies. Hematoxylin and eosin were used throughout, with Levaditi and Giemsa stains on selected tissues.

The acinar structure of the liver was well preserved. The sinusoids were dilated and filled with blood. There were numerous intra-acinar and intracapillary areas of erythropoietic and granulopoietic tissue. The liver cells were large, their nuclei pale and vesicular. There was a moderate periportal infiltration of lymphocytes and granulocytes. Calcareous particles were adherent to and encased within the markedly thickened capsule.

The suprarenal glands presented a slight hyperemia of the zona reticularis.

The heart revealed no abnormality.

The follicles of the thyroid gland were both large and small and lined by cuboidal cells and filled with a well staining colloid. The blood vessels were markedly dilated.

The peritoneal part of the diaphragm was markedly thickened and infiltrated by histiocytes, fibroblasts, multinucleated giant cells and lymphocytes.

The kidneys showed focal areas of interstitial infiltration composed of lymphocytes. In the center of one of these infiltrations was a convoluted tubule with two layers of epithelium. Externally, there was a layer of elongated cells, and the internal layer was formed by large cuboidal cells with huge, round, deeply stained nuclei.

The vessels of the mesentery were patent and of normal structure.

The pancreatic acini were well developed. The islands were large and numerous. The interstitial tissue was of moderate amount. There were numerous interlobular and intralobular accumulations of lymphocytes. In the peritoneal lining were numerous, bluish, granular clumps, histiocytes, round cells and giant cells.

The malpighian corpuscles of the spleen were small. The sinusoids were indistinct, and there was much blood within the pulp, which was moderately cellular. The capsule was thick and edematous, and there were numerous dark blue granular clumps scattered throughout. The deeper part of the capsule was invaded by new-formed capillaries, fibroblasts and eosinophils.

The ovary showed a large number of primitive follicles and a distinct capillary dilatation.

The brain presented no abnormality.



Fig 3—Transverse section just lateral to the perforation showing (a) absence of longitudinal muscle layer and marked thinning of the circular layer, large amount of lymphatic tissue in the submucosa and (b) deeply penetrating crypts of Lieberkuhn, which rest directly on the muscularis, $\times 150$. Hematoxylin and eosin stain.

Sections of the intestines through areas other than those immediately above, below or through the perforation showed nothing abnormal. The lymphoid tissue was normal in amount. The perivascular muscle gaps were located mainly along the mesentery in the small intestine and lateral to the taenia mesenterica in the large intestine. Occasional gaps occurred on the antimesenteric side of the small

intestine. These were normal when compared with the control sections. Longitudinal sections through the perforation showed the following matters of interest. Lateral to the perforation, the muscle layers were well preserved, but there was noticeable an excessively large amount of lymphatic tissue in the submucosa which broke up the muscularis mucosa over large areas. Directly lateral to the perforation, the muscle layer suddenly thinned out, and the longitudinal layer disappeared. The lymphatic tissue here became still more marked in amount, and the mucosal glands penetrated this tissue and rested directly on the muscularis (fig 3). The circular muscle became progressively thinner and thinner

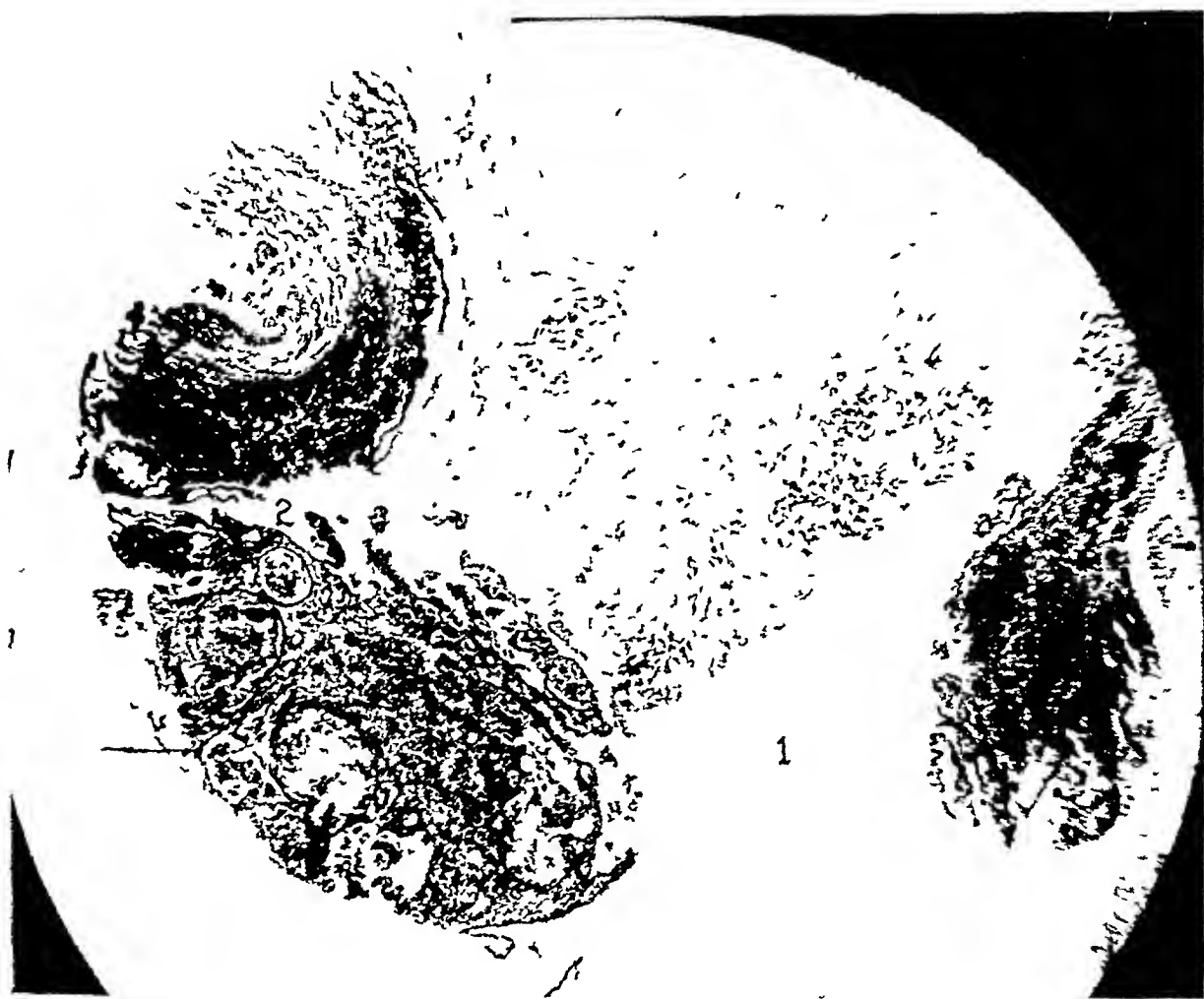


Fig 4—Longitudinal section through perforations showing (1) the major perforation bounded by lymphatic nodules covered by cystic glands and (2) the small perforation through a section of intestine in which the muscularis is absent and the lymphatic tissue and glands are excessively developed, $\times 35$ Hematoxylin and eosin stain

as the lymphoid tissue increased. The next section showed an outpouching of the wall composed of glands and lymphoid tissue. In the next section, this outpouching had ruptured, and the mucosa was reflected sleeve-like about the opening. In this reflected portion, the intestinal glands were large and cystic. Within these cystlike structures, granular debris and polymorphonuclear leukocytes could

be seen. In the next few sections, another perforation was seen at the margin of the reflected portion. This perforation was bounded by lymphatic tissue deeply penetrated by crypts of Lieberkuhn. There was no underlying muscle tissue (fig 4). The succeeding sections showed the main perforation bounded by huge lymphoid masses covered by cystic glands. As the muscle tissue approached the perforations, it ended abruptly (fig 5). Serial transverse sections immediately below the sites of perforation revealed a large amount of lymphatic tissue. The latter occupied more than two thirds of the circumference, and in places the glands of Lieberkuhn were seen to penetrate this tissue down to the muscularis (fig 6). This was not to be found in the sections immediately above

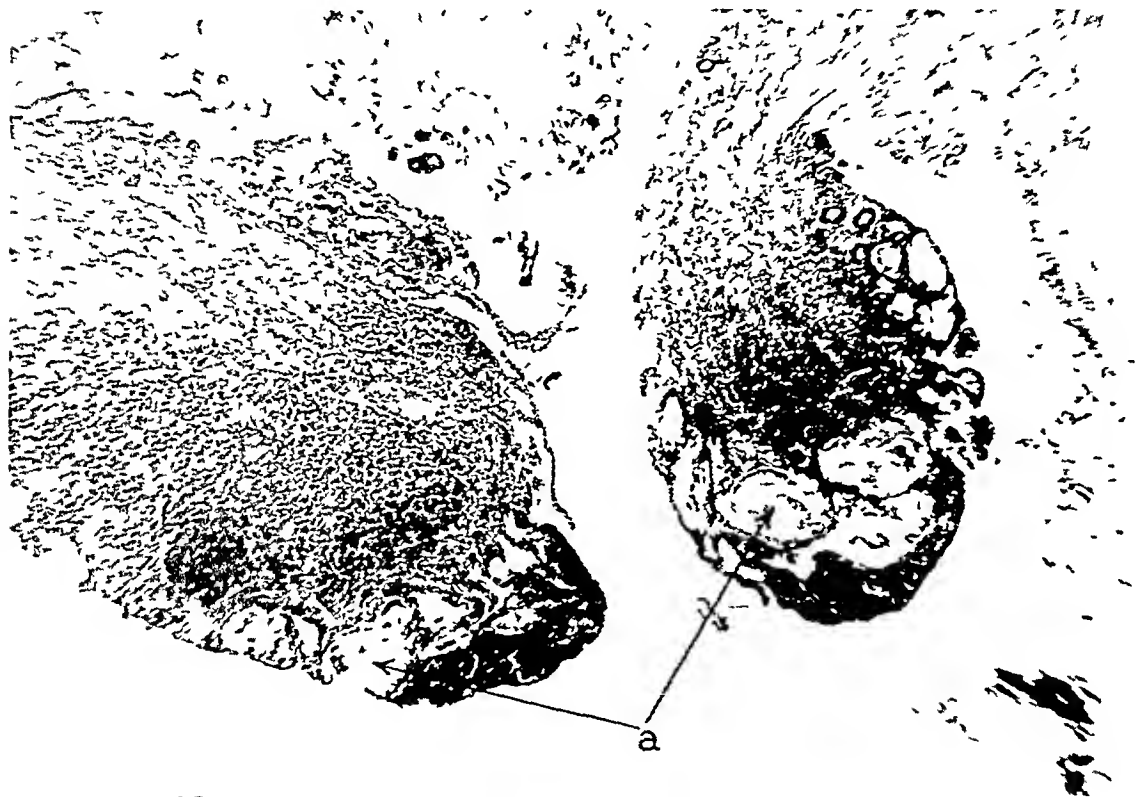


Fig 5—Longitudinal section through middle of perforation showing large lymphatic nodules and (a) cystic glands, $\times 45$

the perforation nor in the sections of this region taken from other infants. Smears from the peritoneal exudate showed a few gram-positive cocci. Levaditi stains of pancreas, kidney and liver were negative for spirochetes.

Summary of Microscopic Examination In addition to a chronic meconium peritonitis with calcification and advanced fibrosis, the outstanding features at the sites of perforation were excessive development of lymphatic tissue, deeply penetrating intranodular crypts of Lieberkuhn, circumscribed disappearance of the longitudinal muscle layer with marked thinning of the circular layer, cystic dilatation of glands of the reflected portions of the intestinal wall and intralymphatic gland proliferations in the segment of intestine immediately below the perforations.

Anatomic Diagnosis—Spontaneous intra-uterine perforation of the lower ileum with eversion of the mucosa, local hyperplasia of the lymphatic tissue at the point of and below the site of perforation with intranodular gland proliferation, ancient meconium peritonitis focal interstitial chronic nephritis and pancreatitis, chronic tumor of the spleen, compression atelectasis of the basal parts of both lungs, erythropoiesis and granulopoiesis in the liver, left inguinal hernia

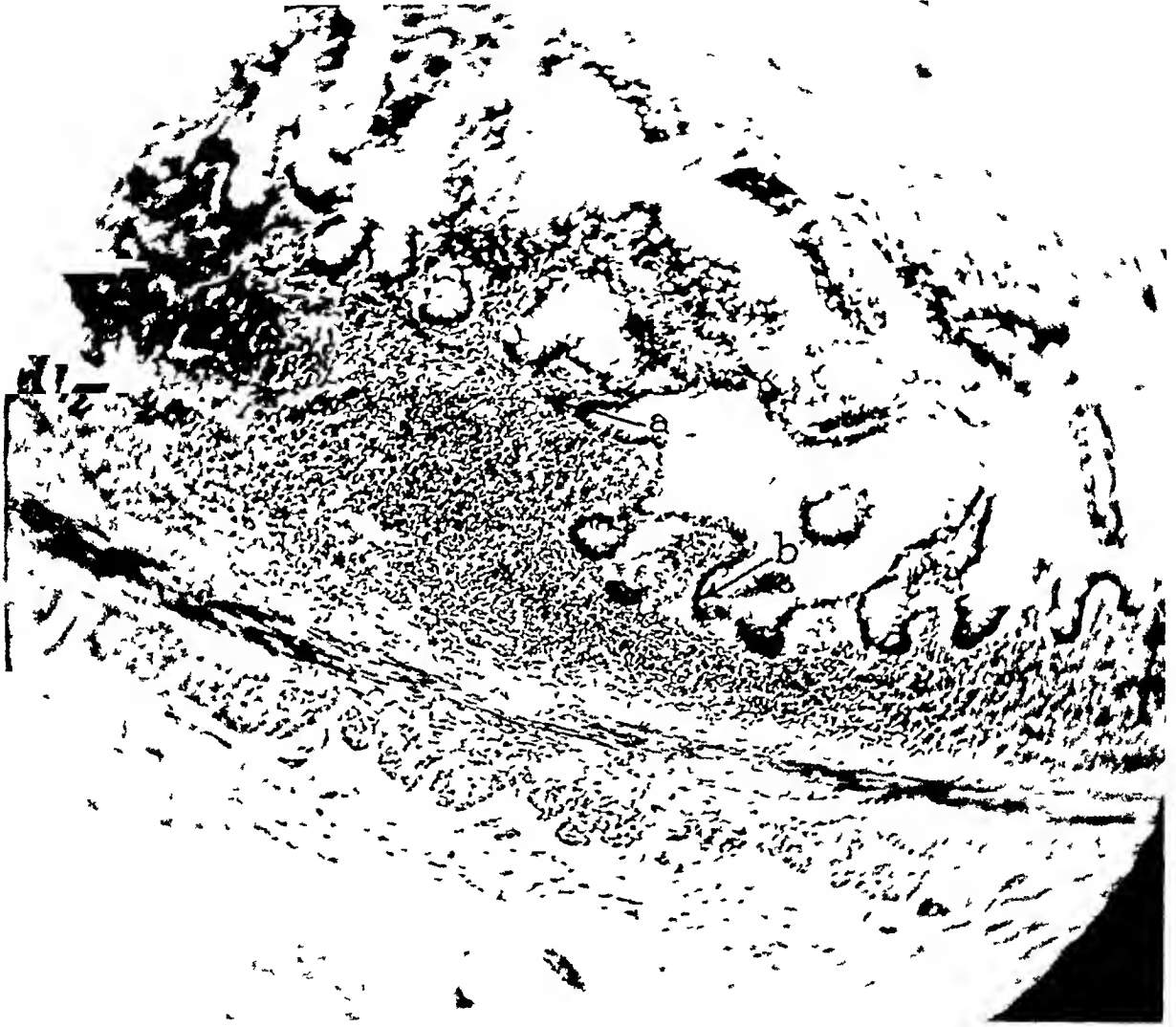


Fig 6—Transverse section through intestine immediately below the perforation showing (a) the large amount of lymphatic tissue and the abruptly interrupted muscularis mucosa and (b) the deep penetration of the former by the crypts of Lieberkuhn

COMMENT

There are numerous factors in the causation of rupture of the intestine in utero. For the purposes of discussion they will be divided into the group associated with obstruction and that without.

Cases with Obstruction—A large percentage of cases of fetal peritonitis are associated with some form of intestinal obstruction.

Thus of 40 cases of meconium peritonitis reported by Rudnew,¹⁵ 22, or more than 50 per cent, were associated with stenosis or atresia of the intestine. As to which is cause and which effect would seem to offer little difficulty from an analysis of the relative frequency. In 1922 Davis and Poynter¹⁸ collected 392 cases of intestinal occlusion (exclusive of rectal) without intestinal perforation. In 103 similar cases, Kreuter¹⁹ found only 10 cases of peritonitis. The explanation of intestinal occlusions has been rather unsatisfactory, as can be gathered from the multiplicity of causes cited. Thus Kuliga,²⁰ Sella,²¹ Peiser²² Davis and Poynter¹⁸ mentioned intussusception, volvulus, vascular maldevelopment, external bands, enteritis, fusion of Kerkring's folds and epithelial proliferation (in the duodenum Tandler²³ and in the small intestine Kreuter¹⁹ and Forssner²⁴). It is therefore not surprising that fetal peritonitis has been also mentioned as a possible cause (Fiedler²⁵ and Theremin²⁶). This is obviously wrong as can be gathered from the foregoing statistics. Complete resolution of peritonitis is impossible. Isolated peritoneal bands are reported in the literature (Flesch²⁷) as evidence of fetal peritonitis. These are without doubt developmental and not inflammatory in origin.

The sites of predilection of stenoses and atresias are duodenum (34 per cent), upper small intestine (15 per cent), ileocecal region (25 per cent), colon (10 per cent) and multiple locations (10 per cent) (Davis and Poynter¹⁸). These figures are somewhat variable (Kuliga²⁰

¹⁸ Davis, D. L. and Poynter C. M. W. Congenital Occlusions of the Intestines with Report of a Case of Multiple Atresia of the Jejunum, *Surg. Gynec. Obst.* **34** 35 (Jan.) 1922.

¹⁹ Kreuter, E. Die angeborenen Verschlüssungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte, *Deutsche Ztschr. f. Chir.* **79** 1 1905.

²⁰ Kuliga, P. Zur Genese der kongenitalen Dunndarmstenosen und Atresien. *Beitr. z. path. Anat. u. z. allg. Path.* **33** 481, 1903.

²¹ Sella, U. Ueber kongenitale Atresia des Darmes und der weiblichen Genitalen und ihr Verhältnis zur fötalen Peritonitis, *Beitr. z. path. Anat. u. z. allg. Path.* **53** 243, 1912.

²² Peiser, A. (footnote 1).

²³ Tandler, J. Zur Entwicklungsgeschichte des menschlichen Duodenum in frühen Embryonalstadien, *Morphol. Jahrb.* **29** 187, 1902.

²⁴ Forssner, H. Die angeborenen Darm und Oesophagus Atresien, *Anat. Hefte* **34** 1 (Juli) 1907.

²⁵ Fiedler cited by Theremin, E. Ueber kongenitale Occlusionen des Dunndarms, *Deutsche Ztschr. f. Chir.* **8** 34, 1877.

²⁶ Theremin, E. (footnote 25).

²⁷ Flesch, H. Beitrag zur Frage der fötalen Peritonitis, *Jahrb. f. Kinderh.* **108** 366 (Mai) 1925.

Braun,²⁸ Farr and Brunkow²⁹) They are exclusive of rectal strictures, which are from one to four times as numerous as all the other occlusions together

An analysis of cases of intestinal obstruction associated with perforation shows that the latter generally occurs just proximal to the obstruction, except in strictures of the rectum, in which the rupture is variably situated from cecum to sigmoid The mechanism of perforation in these cases varies The active peristalsis above an obstruction produces thinning and perforation, whereas volvulus compromises the blood supply with resulting necrosis and perforation

Cases of fetal peritonitis have been described with every type of intestinal occlusion Intussusception in the lower ileum was observed by Chiari,³⁰ Sella²¹ and Ciechanowski and Ginski,³¹ volvulus of the small intestine by Notterbrock³² and Stutzenegger,⁶ simple atresia and rupture by Klokiewicz,³² Martens³³ and recently Westphal³⁴ Obstruction by peritoneal bands is frequent Pfaff³² observed a band which bound the hepatic flexure to the gallbladder and caused a rupture of the distended ascending colon A complete severance of a loop of intestine by a constricting band with perforation of the proximal dilated segment was described by Mackenrodt¹⁴ These bands are no doubt of developmental origin, and are related to atrophied prolongations of Meckel's diverticulum, incompletely obliterated fetal mesenteries, etc Valve-like occlusion of the lumen by mucosal folds with rupture proximally was found in the rectum by Browicz³² and in the ileum by Loebisch³² Angulations of the intestine are responsible for still other cases as reported by Ciechanowski,³¹ in whose case a sharply angulated transverse colon ruptured proximal to the angulation Rudnew¹⁵ and Heyn³² mentioned cases of kinked loops of the ileum which led to perforation The origin of these bands and kinks is to be attributed to torsion and maldevelopment of the mesenteries Imperforate anus has led to innumerable cases of bowel rupture the site of which varied from the ileum (Poelman³⁵) to every part of the colon (cecum,

28 Braun, cited by Koch *Missbildungen von Verengerungen und Verschlüsse*, in Henke and Lubarsch (footnote 2, p 189)

29 Farr, R E, and Brunkow, C W *Congenital Abnormalities of the Intestine*, Arch Surg **11** 417 (Sept) 1925

30 Chiari, cited by Sella (footnote 21)

31 Ciechanowski, S, and Ginski, L K *Zur Frage der kongenitalen Dünndarmatresie*, Virchows Arch f path Anat **196** 168, 1909

32 Cited by Rudnew (footnote 15)

33 Martens, S *Zur Kenntnis der Darmverschlüssen und Verengerungen*, Deutsche Ztschr f Chir **57** 1, 1900

34 Westphal, U *Kasuistischer Beitrag zur fötalen Peritonitis*, Monatschr f Geburtsh u Gynak **66** 245 (June 24) 1924

35 Poelman, cited by Kuliga (footnote 20)

Dienst,³⁶ ascending colon, Pietty,³⁷ hepatic flexure, Bednai,³⁷ and descending colon Lyss³⁷) Genital and urinary atresias are frequently associated with rectal anomalies Without going any further into the complicated question of their origin, one may conclude that the peritonitis of such cases may be simply urinary, as in the case of abnormal communication of the bladder and uterus, or combined urinary and meconium in associated sigmoid rupture or fistula (Olshausen,³⁸ Sella²¹)

Cases without Obstruction—I shall now consider those cases of meconium peritonitis without stenosis or atresia of the intestines They form fully 50 per cent of all the cases of meconium peritonitis An analysis of 23 cases shows that the perforations occur in the colon about twice as frequently as in the terminal ileum The latter is the site of predilection in the small intestine whereas all parts of the colon are equally involved The causes of such perforations are manifold, and will be taken up in succession

Trauma was considered of the utmost importance by Zillner³⁹ He reported 4 cases of death from peritonitis from twelve to fifteen hours after delivery In all these cases there was found a recent meconium peritonitis due to a perforation of the free border of the sigmoid through which the mucosa everted sleeve-like about the opening Zillner³⁹ attributed the rupture to compression of the free sigmoid loop between the lumbar vertebrae and the anterior abdominal wall during labor No microscopic studies were made, and a more definite conclusion, therefore, cannot be drawn None of the numerous recent cases have been attributed to trauma

Meconium stasis as a cause of rupture was first utilized by Paltauf⁴⁰ Paltauf described spontaneous perforations of the colon and sigmoid in five new-born infants These had all been spontaneous easy deliveries Perforations occurred as widely gaping tears of the serosa and muscularis Through these the submucosa and mucosa herniated, and were perforated in some places and remained intact in others There were present therefore all stages of perforation, clearly indicating that the process started from without as a rupture of the outer two layers, with

36 Dienst, A Ueber Atresia Ani congenita, Virchows Arch f path Anat **154** 81, 1898

37 Cited by Dienst (footnote 36)

38 Olshausen, R Zur Aetiologie der fetalen Peritonitis, Arch f Gynak **2** 280, 1871

39 Zillner, E Ruptura flexurae Sigmoides Neonati interpartum, Virchows Arch f path Anat **96** 307 1884

40 Paltauf, A Die spontane Dickdarmruptur der Neugeborenen, Virchows Arch f path Anat **111** 461, 1888

a subsequent herniation of the inner two and then a perforation of the latter. Microscopic examination revealed no ulceration of the mucosa. Serial studies showed the primary change to be an arterial compression, venous dilatation and necrosis of the muscularis at the site of rupture with much reactive infiltration and hemorrhage. Paltauf ascribed these changes to meconium stasis. The explanation of the stasis was not attempted. Hughes⁴¹ described a perforation of a stercoial ulcer in the transverse colon caused by a mass of meconium. Similar cases of meconium obstruction in the terminal ileum were contributed by Bullowa and Brennan,⁴² and Fanconi⁴³ and in the descending colon by Rudnew. A satisfactory explanation of these cases was not offered. Intestinal aplasia, faulty and deficient innervation of the bowel and hypersecretion or deficient secretion of the intestinal glands are some of the many theories. In only two cases were adequate explanations forthcoming.

Landsteiner,⁴⁴ in 1905, explained intestinal obstruction in a newborn infant on the basis of a putty-like column of meconium which was intimately adherent to the mucosa of the terminal ileum. The bowel above was hypertrophied, and the colon was empty and contracted. The pancreas showed extensive interstitial fibrosis and cellular infiltration. He concluded from the studies of Zweifel⁷ and Langendorff¹⁰ on fetal physiology that the absence of the pancreatic secretion in some way deprived the meconium of essential elements, probably enzymes, in addition to water, and the meconium thus became fatty and putty-like. Such a meconium was difficult to propulse and piled up in the ileocecal region. An almost identical case was recently contributed by Kornblith and Otani.⁴⁵ In their case, the pancreatic duct was stenosed and the putty-like meconium had caused ulceration of the ileum and a rupture of the ascending colon. It is worthy of note that an identical mass of putty-like adherent meconium caused obstruction in the terminal ileum in a case reported by Fanconi.⁴³ The pancreas in his case was normal, but the liver showed evidence of obstruction of the bile ducts due to an aplasia of the large ducts. Deprivation of bile can apparently produce a fatty meconium similar to that produced by deprivation of pancreatic secretion (similar to conditions in adults).

41 Hughes, E. E. Acute Intestinal Obstruction Due to Inspissated Meconium, *Brit J Child Dis* **19** 32 (Jan-March) 1922.

42 Bullowa, J. G., and Brennan, R. E. Intra-Uterine Intestinal Obstruction from Inspissated and Impacted Meconium, *J A M A* **73** 1882 (Dec 20) 1919.

43 Fanconi, G. Fünf Fälle von angeborenen Darmverschluss, Duodenumatresien, Duodenalstenose, Meconium Ileus, *Virchows Arch f path Anat* **229** 207, 1921.

44 Landsteiner, K. Darmverschluss durch eingedicktes Meconium Pancreatitis, *Centralbl f allg Path u path Anat* **16** 903 (Nov 30) 1905.

45 Kornblith B. A., and Otani, S. Meconium Ileus with Congenital Stenosis of Main Pancreatic Duct, *Am J Path* **5** 249 (May) 1929.

Fetal intestinal infections as a cause of intestinal perforations are obscure Tolmatschew ⁴⁶ described a meconium peritonitis in a 3 days old child produced by the perforation of a small gummatous ulcer Cases of late fetal and intrapartum appendicitis were reported by Jackson ⁴⁷ and Hill and Mason ⁴⁸ But a meconium peritonitis was not present

Primary vascular insufficiency as a cause for bowel perforation was first advanced by Helbing ⁴⁹ and supported by Spies ⁵⁰ This conception has been stressed by a number of authors as a cause for intestinal atresia (Wyss, ⁵¹ Nobling, ⁵² Jaboulay, ⁵² and Davis and Poynter ¹⁸) These vascular changes are no doubt secondary to the atresia, and Spies ⁵⁰ offered proof in support of his conception For his own case, he could not decide whether the condition was due to torsion of the intestine or fetal infection of maternal origin

There is an important relation between congenital diverticula and meconium peritonitis Meckel's diverticulum plays an important rôle in fetal obstructions and incarcerations This has been reviewed by Halstead, ⁵³ Porter, ⁵⁴ Koch ⁵⁵ and others Meconium peritonitis due to a ruptured Meckel's diverticulum was described by Genersich ⁵⁶ and Orth ⁵⁷ Recently Hunter ⁵⁸ and Shukowski ⁵⁹ reported gangrenous Meckel's diverticulum in new-born infants The other congenital

⁴⁶ Tolmatschew, cited by Peiser (footnote 1)

⁴⁷ Jackson, W F A Case of Prenatal Appendicitis, *Am J M Sc* **127** 710 1904

⁴⁸ Hill, W B, and Mason C C Prenatal Appendicitis with Rupture and Death, *Am J Dis Child* **29** 86 (Jan) 1925

⁴⁹ Helbing, T Ueber fotale Peritonitis nebst einem kasuistischen Beitrag, Inaug Dissertation, Freiburg, 1908

⁵⁰ Spies, Paul Ueber fotale Peritonitis, Inaug Dissertation, Heidelberg, 1917

⁵¹ Wyss, M O Ueber kongenitale Duodenal-Atresien Beitr z klin Chir **26** 631, 1900

⁵² Cited by Sella (footnote 21)

⁵³ Halstead, A E Intestinal Obstruction from Meckel's Diverticulum, *Ann Surg* **35** 471 (Jan-June) 1902

⁵⁴ Porter, M F Abdominal Crises Caused by Meckel's Diverticulum, *J A M A* **45** 883 (Sept 23) 1905

⁵⁵ Koch, W Magen und Darm-Missbildungen III Erhaltenbleiben embryonaler Anlagen, in Henke and Lubarsch (footnote 2, p 175)

⁵⁶ Genersich, A Bauchfellentzündung beim Neugeborenen infolge von Perforation des Ileums, *Virchows Arch f path Anat* **126** 485, 1891

⁵⁷ Orth, cited by Genersich (footnote 56)

⁵⁸ Hunter, W C Perforated Gangrenous Meckel's Diverticulum in a New Born Infant, *Am J Dis Child* **35** 438 (March) 1928

⁵⁹ Shukowski, cited by Hunter (footnote 58)

diverticula have been recently review by Evans,⁶⁰ who reported their presence in all parts of the intestine. There were, however, none which were associated with meconium peritonitis.

Acquired diverticula are of utmost importance in adult pathology. Although denied by some (Hartwell and Cecil⁶¹), such diverticula are almost always of the false type, that is, they consist from the onset of hernial protrusions of the mucosa through the other layers of the intestinal wall. As early as in 1869, Klebs⁶² emphasized their relation to the interruption of the muscularis produced by the entrance of the mesenteric vessels in the small intestine. He believed that traction on the vessels produced these mucosal herniations. Hansemann⁶³ described 400 diverticula into the mesentery of the small intestine of an old man and laid stress on the importance of pulsion. Graser⁶⁴ restudied the diverticula in the sigmoid and found the presence of microscopic herniations of the mucosa into the perivascular connective tissue sheaths. These patients were particularly chosen because of concurrent general venous or portal obstruction. He attributed great importance to intermittent dilatation of the veins in the production of large muscle gaps through which herniations could readily take place. This view was rejected by Sudsuki,⁶⁵ who found sigmoid diverticula more frequent in cases without than with venous obstruction. The general consensus (Telling and Gruner⁶⁶) is that pulsion by constipation and gas is effective in producing these herniations, between the mesenteric leaves in the small intestine and between the taenia mesenterica and the two anterior free taenia in the colon (Drummond⁶⁷).

The age at which these sacculi occur is usually late. But they have been reported to occur as early as at the age of 7 (Aschhurst⁶⁸).

60 Evans, A. Developmental Enterogenous Cysts and Diverticula, *Brit J Surg* **17** 34 (July) 1929.

61 Hartwell, J. A., and Cecil, R. L. Intestinal Diverticula, a Pathological and Clinical Study, *Am J M Sc* **140** 174 (July-Dec) 1910.

62 Klebs, cited by Hartwell and Cecil (footnote 61).

63 Hansemann, V. Ueber die Entstehung falscher Darmdivertikel, *Virchows Arch f path Anat* **144** 400, 1896.

64 Graser, E. Ueber multiple falsche Darmdivertikel in der flexura Sigmoidea, *Munchen med Wchnschr* **46** 721 (May) 1899.

65 Sudsuki, K. Ueber Divertikel am S. Romanum, *Arch f klin Chir* **61**: 708, 1900.

66 Telling, W. H. M., and Gruner, O. C. Acquired Diverticula, Diverticulitis and Peri-Diverticulitis of the Large Intestine, *British J Surg* **4** 468, 1916-1917.

67 Drummond, H. Sacculi of the Large Intestine with Special Reference to Their Relations to the Blood Vessels of the Bowel Wall, *Brit J Surg* **4** 407, 1916-1917.

68 Aschhurst, cited by Hartwell and Cecil (footnote 61).

Diverticula of this character are important from their frequency of perforation. Peritonitis is not a rare complication. But that such diverticula or sacculi can occur in the fetus and by rupturing produce meconium peritonitis was first brought out by Rudnew,¹⁵ who described 2 cases of meconium peritonitis. His first case concerned a stillborn fetus of 6 months, showing a well calcified fetal peritonitis and a focal necrosis of the antimesenteric portion of the ileum, 21 cm from the ileocecal valve and just above a sharp end in the bowel. The ileum above was dilated, the ileum below contracted. As the cause of the necrosis he found two mucosal herniations into the mesentery. These had ruptured, and the escaped meconium had compressed the vessels. The increased intra-intestinal pressure had produced the mesenteric herniations. His second case concerned a full term infant that died on the fourth day. There was free meconium in the peritoneal cavity issuing from a perforation in the middle of the transverse colon. The splenic flexure, descending colon and sigmoid were distended and thinned by a large amount of meconium. The transverse and ascending colon were hypertrophic but contracted. The site of perforation was seen microscopically as a ruptured mucosal herniation. Further sections showed muscular gaps produced by vessels entering into the bowel, which were as much as 10 mm in diameter. The vessels were so dilated as to appear cavernous. Rudnew,¹⁵ like Graser,⁶⁴ demonstrated early stages of diverticulum formation as mucosal herniations into the perivascular spaces. The actual herniation was produced through increased intracolonic pressure, as shown by the hypertrophy of the muscle of the transverse colon. No actual obstruction was present, and Rudnew¹⁵ assumed faulty innervation of the descending colon. He also concluded that the excessive development of the vessels had produced abnormally large gaps in the muscularis through which mucosal herniations readily took place. He further demonstrated similar but smaller muscle gaps in his first case.

Rudnew's¹⁵ cases parallel the adult condition perfectly, showing herniations at the mesenteric site in the small intestine and antero-laterally in the large intestine. Recently, Fischer⁶⁹ reported an identical case of ruptured diverticulum in the transverse colon and described similar muscle gaps in the colon. Kornblith and Otani⁴⁵ found the gaps produced by the entering vessels to be as wide as the whole muscle wall itself.

Antimesenteric herniations can also take place in the small intestine. Froboese⁷⁰ described three cases of meconium peritonitis due to pin-

69 Fischer, A. E. Case of Fetal Peritonitis Following Spontaneous Rupture of the Large Intestine. *Am J Dis Child* **36** 774 (Oct) 1928.

70 Froboese, C. Ursache der fetalen Peritonitis (Meconiumperitonitis), *Virchows Arch f path Anat* **269** 595, 1928.

point perforations of the antimesenteric border of the lower ileum. In one of these cases, he observed wide muscle gaps and accepted Rudnew's¹⁵ conception. It is to be noted, however, that increased pulsion is the important factor in the production of these diverticula, and in the cases of Fibboese¹⁶ no form of obstruction was present and no evidence for increased intra-intestinal pressure which could produce these herniations. He admitted that he found nothing in his first two cases, and only muscle gaps (a normal occurrence) in his third case. Histologic data on the conditions at the site of perforation are not given. Finally von Sury⁷¹ in attempting to explain a case of meconium peritonitis resulting from a ruptured rectum, came to the conclusion that local aplasia was the only acceptable explanation, since, in his opinion meconium stasis alone did not suffice to cause rupture. No histologic studies of the site of perforation were made.

Of the numerous causes for intestinal perforation in the fetus and the new-born infant reviewed in this article, not a single one seems adequate for my case. There was no form of obstruction and the muscularis above the perforation was not hypertrophic. The pelvic organs were normal. There was also no stasis of meconium, the latter was not abnormal in amount, consistency or distribution. The other organs were normal. There was no indication of syphilis. The Wassermann reaction of the blood was negative and the Levaditi stains were negative.

The vessels supplying the segment of perforated bowel were patent and normal. Neither Meckel's diverticulum nor the congenital diverticula described by Evans⁶⁰ were present. The possibilities of fetal enteritis and focal aplasia will be discussed later.

As previously mentioned, the essential observations at the sites of perforation were excessive development of lymphatic tissue, deeply penetrating intranodular crypts of Lieberkuhn which rested on the muscularis, circumscribed disappearance of the longitudinal muscle layer with marked thinning of the circular layer, cystic dilatation of the glands of the reflected portions of the bowel and intra-lymphatic glandular proliferations in the segment of bowel immediately below the perforations.

I believe that the glands invading the lymphatic tissue and the excessive lymphatic tissue are of utmost importance in the explanation of the present case. Lauche⁷² recently extensively reviewed these intranodular gland proliferations. In addition to their occurrence as a

71 Von Sury, K. Die spontane Darmruptur bei Neugeborenen, *Vrtljschr f gerichtl Med* 2 91 1912

72 Lauche A. Die Heterotopien des Ortsgehorigen Epithels im Bereich des Verdauungskanal, *Virchows Arch f path Anat* 252 39, 1924

sequel of ulcerative processes anywhere within the gastro-intestinal tract (Lohlein,⁷³ Konjetzny⁷⁴), comparative and embryologic studies have established them as not infrequently of normal occurrence. Lauche⁷² traced the origin of these glandular proliferations to the anti-mesenteric diverticula in 5 to 32 mm embryos described by Lewis and Thyng⁷⁵. From the available literature, he described their constant normal presence in *Echidna* (Klaatsch⁷⁶), their occasional occurrence in a wide range of mammals, in full-term fetuses and young children (Meyer⁷⁷) and in the appendix (Lubarsch⁷⁸) and colon (Orth⁷⁹) of adults.

Lauche believes these intralymphatic submucosal gland proliferations to be due to the breaking up of the muscularis mucosa by the lymphatic nodules. But if one is to accept his view that these penetrating glands are derived from the diverticula described by Lewis and Thyng⁷⁵ as occurring in 5 to 32 mm embryos, their development precedes that of the lymphatic tissue by a long period, since the latter develops in the embryo at 240 to 300 mm.

I therefore explain the excessive lymphatic tissue as a response to the abnormal persistence of these diverticula just as occurs when the invasion is secondary to an ulcerative process. The observations in my own case justify this conception. Both at the site of perforation and below it, the glands penetrate deeply and are surrounded by excessive amounts of lymphatic tissue. The circumscribed disappearance of the longitudinal muscle fibers and the marked thinning of the circular layer are probably the result of pressure from the large accumulation of lymphatic tissue. The changes at the second small perforation show clearly the disappearance of the muscle tissue and at the large perforation how excessively the lymphoid tissue may develop. These areas of diminished strength then ruptured and permitted the exit of meconium. The perforation probably occurred as the rupture of a deeply penetrating gland.

73 Lohlein, cited by Lauche (footnote 72)

74 Konjetzny, A. I. Ueber die Beziehungen der chronischen Gastritis mit ihren Folgeerscheinungen und des chronischen Magenulcus zur Entwicklung des Magenkrebses, *Beitr. z. klin. Chir.* **85** 455, 1913.

75 Lewis, F. T., and Thyng, F. W. The Regular Occurrence of Intestinal Diverticula in Embryos of Pig, Rabbit and Man, *Am. J. Anat.* **7** 505, 1907-1908.

76 Klaatsch, cited by Lauche (footnote 72)

77 Meyer, R., in discussion of Lubarsch, O. Ueber heterotope Epithelwucherungen und Krebs, *Verhandl. d. deutsch. path. Gesellsch.* **10** 216, 1906.

78 Lubarsch, cited by Lauche (footnote 72)

79 Orth, J. Ueber die Beziehungen der Lieberkuhn'schen Krypten zu den Lymphknoten des Darms unter normalen und pathologischen Verhältnissen, *Verhandl. d. deutsch. path. Gesellsch.* **3** 135, 1901.

The cystic character of the glands in the portion of mucosa reflected about the perforation is probably secondary to the inflammatory processes in the peritoneum to which the glands were exposed and not to a primary enteritis, for which there is no proof. To speak of local aplasia of the muscularis is too indefinite.

Although histologic studies of intestinal perforations are few, there are none on record in which observations similar to mine have been made. Whether, therefore, the latter are unique or whether further study will reveal them as of more common occurrence remains to be seen.

SUMMARY

A case of meconium peritonitis due to a perforation in the lower ileum is reported. At the site of perforation were excessive development of lymphatic tissue, deeply penetrating crypts of Lieberkuhn which rested directly on the muscularis and a local sharply circumscribed absence of the longitudinal muscular layer, marked thinning of the circular muscular layer and cystic dilatation of the glands of the mucosa reflected about the perforation. Below the perforation was a large amount of lymphatic tissue with deeply penetrating crypts of Lieberkuhn, which here also rested directly on the muscularis.

The sequel of events is conceived to be primarily a persistence of fetal antimesenteric diverticula. In response to these, excessive lymphatic tissue developed, which caused pressure atrophy of the muscularis. Peristalsis ruptured this local area of diminished resistance. The cystic character of the glands is attributed to the inflammatory processes in the peritoneum.

The literature is reviewed with reference to the etiology of meconium peritonitis.

A COMPARISON OF CERTAIN INTRANUCLEAR INCLUSIONS FOUND IN THE LIVERS OF DOGS WITHOUT HISTORY OF INFECTION WITH INTRANUCLEAR INCLUSIONS CHARACTERISTIC OF THE ACTION OF FILTRABLE VIRUSES *

E V COWDRY
AND
GORDON H SCOTT
ST LOUIS

In connection with the study of intranuclear inclusions produced in the hepatic cells of man and monkeys by the virus of yellow fever (Cowdry and Kitchen¹), many other hepatic lesions were examined for purposes of control. Among these were many preparations, and blocks of tissue which we sectioned and stained for ourselves, from the livers of dogs kindly given to us by Dr Otto Schwarz and Dr W J Dieckmann. The dogs had been employed in experiments designed to produce lesions like those characteristic of human cases of eclampsia (Dieckmann²). What interested us particularly was the discovery in some of them of what seemed to be typical intranuclear inclusions. Indeed, the bodies were so like those formed in virus diseases as to raise the question of whether a virus was not actually at work in the tissues.

A detailed study of these inclusions promised to yield interesting results, for, if it should be shown that the inclusions were in fact a manifestation of virus action, the possibility that they were caused by a virus not hitherto recognized would have to be tested. Thus far, viruses affecting by preference endodermal cells, particularly the cells of the liver are rare. We know of only one, namely, that of yellow fever. The discovery of another in a common laboratory animal would afford valuable opportunities for experimentation. Conversely, if it should be ascertained that the inclusions merely result from the experimental conditions imposed on the liver, the condition would be still more interesting. It would constitute the only known case of such

* Submitted for publication, Nov 22, 1929

* From the Anatomical Laboratory of Washington University School of Medicine

1 Cowdry, E V, and Kitchen, S F. Intranuclear Inclusions in Yellow Fever, *Science* **69** 252, 1929

2 Dieckmann W J. The Hepatic Lesion in Eclampsia, *Am J Obst & Gynec* **17** 454, 1929. Further Observations on the Hepatic Lesion in Eclampsia, *Am J Obst & Gynec* **18** 757, 1929

intranuclear inclusions being found in the absence of virus and would act as a corrective against the prevalent conception, which at present has everything in its favor, that inclusions of this general type point rather clearly to the action of a virus

Obviously, the first step was to determine just how close the resemblance actually is between these as yet unknown inclusions in dogs and others which have definitely been proved to be caused by filtrable and as yet ultravisible agents in other tissues. Our results in this direction are presented in this paper and the likelihood of the presence of a hitherto unrecognized filtrable virus is discussed

INCIDENCE OF THE INCLUSIONS

The livers of sixty-eight dogs were available for examination. The general course of treatment in all of them was to give "a full meal of raw meat daily followed by the injection of tissue fibrinogen or lung extract in the general circulation 1 hour later, the dosage varied from 0.5 to 3 cc of tissue fibrinogen or lung extract. Frequently, after the injection into the general circulation, the animal would cry out, urinate, have evacuations from the bowels and develop convulsions. The animals were sacrificed at varying periods of from two to seven days, they were always sacrificed when the symptoms produced by the injections were marked, so as not to have the animal die during the night" (Dieckmann³)

Careful study revealed typical intranuclear inclusions in only two, which means that their incidence is lower than was at first supposed. The history of these dogs is as follows:

Dog 67, male, weighing 6,250 Gm, was fed raw meat on March 26, 1929. One hour later, the animal was given 1 cc of a saline extract of ground up calf lung by intracardiac injection. The dog voided, showed some signs of shock and died three hours later.

Dog 36, female, weighing 6,810 Gm, was fed regularly on a diet of raw meat and given daily injections of fibrinogen for nine days beginning with 1.5 cc and gradually increasing to 3 cc. The dog died two hours after the ninth dose.

There is no reason to suppose that they were treated differently from the others, except, perhaps, in respect to details which would not seem to be the controlling factors and which were so insignificant as to escape mention in the protocols. To check this possibility, we tried to secure other livers laden with intranuclear inclusions by duplicating the experimental procedures. In this and all our other experiments, ether was used as an anesthetic. Five futile attempts left us with the impression that the intranuclear inclusions might not result from the experiments at all. We then made a comprehensive study of the lesions

³ Dieckmann (footnote 2, second reference)

in the livers containing the intranuclear inclusions to determine in just which respects they corresponded and differed from the large majority of the series

The intranuclear inclusions were present in approximately 80 per cent of hepatic parenchymal cells and 20 per cent of endothelial cells in dog 67. In the other dog, the corresponding percentages were about 20 and 5. In both dogs, their presence was definitely associated with hemorrhage and necrosis in the central and middle thirds of the hepatic lobules and with an increase in the number of phagocytic cells, especially polymorphonuclears and macrophages. There was also rather marked swelling of the endothelium of the sinusoids. The livers of several other dogs, which were modified in much the same way, contained no intranuclear inclusions. Since, for this reason, the hypothesis seemed strengthened that the special experiments of Dieckmann might not be the determining influences in the production of the inclusions, the livers of still other dogs were examined to see whether the inclusions could be found in dogs which had not been made the subject of such experiments. These control livers were from several sources: four from dogs treated with carbon tetrachloride by Dr. Paul D. Lamson, four from dogs into which we had injected, intrahepatically, active herpetic virus in order to determine whether the inclusions under investigation looked like those characteristic of herpes, as will be mentioned later, eight from dogs into which had been injected, intrahepatically, ground up liver substance in series, as will be described subsequently, and three from dogs employed in various experiments by Dr. I. Y. Olch, which were also quite different from those of Dieckmann.

In none of these nineteen livers were any of the inclusions seen, but these negative observations were not sufficiently numerous to settle positively the question of whether the incidence of the inclusions was related to Dieckmann's experiments. No inclusions resembling them were observed in the livers of fifty monkeys experimentally infected with the virus of yellow fever or in the livers from fifty patients who had died from the disease.

Whether similar intranuclear inclusions occur in tissues other than the liver we cannot at present state, because only the liver with now and then a section of kidney and spleen was available from each dog for examination.

PROPERTIES OF THE INCLUSIONS

The inclusions presented the features usually exhibited by intranuclear inclusions in virus diseases. The livers from the two dogs with inclusions had been fixed in Kaiserling's fluid, which would not be likely to alter their subsequent tinctorial properties, but which was

not favorable for microchemical analyses. Like other intranuclear inclusions they were acidophilic, staining by preference with "acid" dyes, such as eosin, erythrosin and phloxin, so that they appeared red or pink in contrast with the blue-colored basophilic chromatin after staining with eosin-methylene blue, hematoxylin and eosin, Giemsa stain and other similar combinations.

Topographically, the intranuclear inclusions occupied the centers of the affected nuclei as may be seen by reference to figure 1. In field 1, an inclusion-laden nucleus in an hepatic cell is visible a little to the right of the center. The inclusion is dark and looks homogeneous. It is separated from the nuclear membrane by a characteristic area of rarefied nucleoplasm which is not stained. It can be seen, also, that the chromatin is irregularly margined on the nuclear membrane being rather more dense above and to the left.

In the center of field 2, an endothelial nucleus is represented, likewise carrying an inclusion, the morphology of which is molded after that of the limiting nuclear membrane. The surrounding clear area and the irregular margination of chromatin are well shown.

The lower view (3) shows three nuclei with typical inclusions all in hepatic cells. The one to the left contains an almost spherical inclusion, the outlines of which are clearcut. The inclusion is eccentrically placed. A little above and to the left of it, the nuclear membrane appears to be thickened, a change which is caused by the disintegrating nucleolus being closely applied to it. The other two nuclei are contained within a single hepatic cell and are to the right of the center of the figure. The outlines of the cell membrane can be roughly determined. One of these nuclei presents two inclusions, which is unusual. It will be observed, however, that the actual amount of inclusion material is approximately the same in the two nuclei. The outlines of the inclusions are not so sharp as in the case of those already mentioned. Delicate and tapering strands of substance seem to pass out from them across the clear area toward the nuclear membranes.

Inclusions in many stages of formation were always visible even in a single slide, though those which have been described predominated. With care, the seriation in changes could be made so complete that we can speak with confidence of a process taking place. On the one hand, there were presumably the early stages which seemed to be most numerous in the peripheral parts of the lobules. These were characterized by the accumulation in the central parts of the nuclei of minute acidophilic particles which became more and more tightly packed together until they fused into a single mass, at the same time, the nucleolus was displaced to one side, and the ground substance of

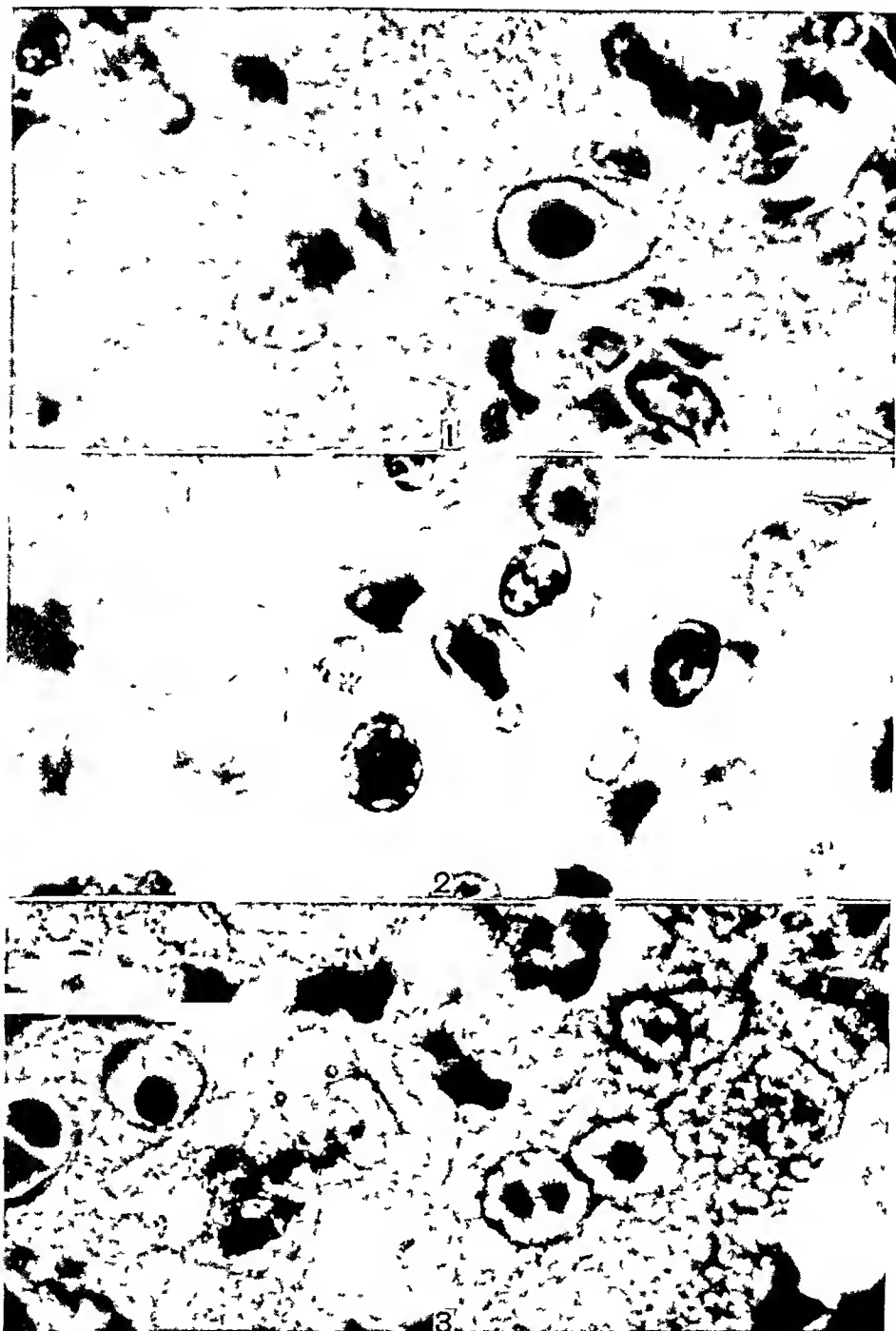


Fig 1—(1) A little to the right of the center, a nucleus of an hepatic cell is seen containing a well marked, centrally placed inclusion, which is separated from the nuclear membrane by a halo of relatively unstained nucleoplasm, $\times 1,200$

(2) Almost in the middle of the photograph is an endothelial nucleus containing an inclusion the form of which corresponds rather closely to the shape of the nucleus itself. Basophilic chromatin is margined irregularly on the nuclear membrane, $\times 1,200$

(3) Several nuclei containing inclusions are shown. In the nucleus to the left the inclusion is almost spherical and is excentrically placed, being in contact on one side with the nuclear membrane. Slightly lower and to the right are two nuclei in contact. One of these has a double inclusion and the other a single one. The outlines of the inclusions are more irregular with faint strandlike extensions of material toward the nuclear membrane, $\times 1,200$

the nucleus became cleared of basophilic chromatin, which was condensed with the remains of the nucleolus, on the surface of the nuclear membrane

On the other hand there were more advanced stages in the process, which by contrast were chiefly found in the central areas of the lobules. We have noted the fact that accompanying the inclusions there was a marked central necrosis. As the change in the nuclei proceeded beyond the stages represented in our photomicrographs, the inclusions enlarged further and the nuclei shrank slightly, so that a point was reached when the inclusions occupied almost the entire intranuclear space. Apparently, while this was happening the basophilic chromatin, absorbed on the nuclear membrane became still more irregular in disposition, being heaped up in some parts and wholly absent in others.

Finally the nuclear membrane disappeared, often by lysis, but occasionally by rhexis and the acidophilic material making up the inclusion could be distinguished with difficulty in the necrotic cytoplasm, which had also undergone an acidophilic change. In the parts of the lobules in which necrosis was most marked there were many macrophages and polymorphonuclears, which probably helped to remove the debris.

It is to be noted that these inclusions were different and distinct from certain intranuclear crystals described by Szymonowicz and Macallum⁴ and illustrated by a figure from a "Preparation of Browicz," which they thought to consist of methemoglobin. We found these crystals, often abundantly in 22 per cent of the dog livers examined, that is to say both in Dieckmann's series and in our other animals. They were hexahedra or pentahedra and from two to three times as long as they were broad. The maximum length measured was 25 microns the average being about 10 microns. Like the inclusions, they stained with eosin and other "acid" dyes and when not colored artificially were unpigmented. They were often surrounded by halos of clear nucleoplasm, and as they were formed, the basophilic chromatin, with the nucleolus, was displaced toward the nuclear membrane, but was not adsorbed irregularly on its surface. When they were cut through their long axis, the morphology of the inclusions and the stretching out of the nucleus were distinctive. It was only when cut in cross-section that, at first sight, they sometimes suggested inclusions caused by a filtrable virus. But in such cases careful examination always revealed plane surfaces and angles and the nuclei did not become necrotic.

⁴ Szymonowicz, L., and Macallum, J. B. Textbook of Histology, Philadelphia and New York, Lea Brothers & Company, 1902

COMPARISON OF THE INCLUSIONS WITH THOSE CAUSED
BY FILTRABLE VIRUSES

Since much work on virus diseases has been done in our laboratory, material was at hand sufficient for a direct comparison of the inclusions with those typical of yellow fever, herpes, chickenpox, Borna disease, submaxillary disease and virus III disease. As far as we could tell, there was no clearcut microchemical difference in the materials involved, so that our observations were chiefly morphologic and topographic.

There was no possibility of confusing the inclusions with those in the liver characteristic of yellow fever, with which we were primarily concerned. They were of a much denser consistency and they were not made up of discrete colony-like masses of particles separated from each other by stretches of clear nucleoplasm. Furthermore, as they developed the nucleoli were soon destroyed, whereas in yellow fever the nucleoli persist. In a paper by Cowdry and Kitchen,⁵ there is a series of photomicrographs of inclusions typical of yellow fever taken at a higher magnification than those which illustrate this paper. A comparison of the two will show how definite are the differences mentioned.

In the case of herpes, we first took some H. F. herpetic virus in a rabbit's brain which had been preserved in glycerin and passed it intracerebrally in the usual way into a second rabbit. This animal soon exhibited the classic symptoms of herpetic encephalitis, and from it we secured fresh virus, which we injected intrahepatically into two dogs. After forty-eight hours had elapsed, the dogs were chloroformed and fragments of livers from the sites of injection were prepared histologically, but no herpetic intranuclear inclusions were found. The experiment was repeated, fresh virus being again prepared from the glycerinated virus. This time it was injected intrahepatically into three dogs, and the tissues were removed for examination from two of them after seventy-two hours and from the third after eighty-four hours, but again no inclusions were seen.

We were consequently obliged to use as controls for the comparison, not the livers of dogs, but the livers of two rabbits and of one monkey (*Cebus hypoleucus*), into which in the study of intranuclear inclusions in yellow fever, the same herpetic virus had been successfully injected. We observed that the unknown inclusions in our dogs differed from these herpetic inclusions in structure. They were much denser, and we did not find a stage corresponding to the almost complete filling up of the nucleus with acidophilic particles of rather variable size seen in herpetic infections. The associated nuclear changes, however, had this in common that in both the nucleoli were early destroyed, and there was

⁵ Cowdry, E. V., and Kitchen, S. F. Intranuclear Inclusions in Yellow Fever, *Am. J. Hyg.*, to be published.

a margination of basophilic chromatin. But this margination of chromatin was more marked in herpes. For other details, reference should be made to the photomicrographs of herpetic inclusions published by Goodpasture and Teague⁶ and by Goodpasture.⁷

The comparison with the inclusions in chickenpox is not so valuable for the reason that the affected cells were so different, liver cells as compared with cells of the skin. The inclusions differed in much the same way as they did from those in herpes, but it does not follow that if the condition which we are investigating is due to a filtrable virus, and further that if this virus can be induced to act on the skin, that the inclusions produced will exhibit the same points of resemblance and of difference, for the character of the inclusions in virus diseases is governed not only by the kind of virus, but also by the type of cell responding to it.

The inclusions were compared with those characteristic of Borna disease only as the latter were seen in the nuclei of nerve cells. The necessary material was kindly given to us by Dr I. A. Galloway of the National Institute for Medical Research, London, England. Like the inclusions in Borna disease, the unknown inclusions in our dogs were rounded acidophilic bodies surrounded by a zone of rarefied nucleoplasm, but here the resemblance ended, for destruction of nucleoli and complete margination of basophilic chromatin were not to be observed in Borna disease (Nicolau, Dimancesco-Nicolau and Galloway⁸).

The inclusions in dogs were much smaller than those produced by the submaxillary virus in the duct cells of the submaxillary gland, and rather larger than the inclusions which resulted when the same submaxillary virus was injected into the brain. In the former situation, the submaxillary inclusions were less dense, but in the latter they seemed to be of about the same density as the inclusions which we are studying in dogs. Photomicrographs of the submaxillary inclusions taken with the same optical combination yielding a magnification of 2,000 diameters will be available for comparison in a paper by Pearson.⁹

6 Goodpasture, E. W., and Teague, O. Experimental Production of Herpetic Lesions in Organs and Tissues of the Rabbit, *J. M. Research* **44** 121 (plate 44, figs 3-7) 1923.

7 Goodpasture, E. W. The Axis-Cylinders of Peripheral Nerves as Portals of Entry to the Central System for the Virus of Herpes Simplex in Experimentally Infected Rabbits, *Am. J. Path.* **1** 11 (plate 3, figs 1-3) 1925.

8 Nicolau, S., Dimancesco-Nicolau, O., and Galloway, I. A. Étude sur les septenévrites à ultra virus neurotropes, *Ann. de l'Inst. Pasteur* **43** 1 (plate 1, fig 1) 1929.

9 Pearson, E. F. Cytoplasmic Inclusions Produced by the Submaxillary Virus, to be published (figs 1 to 3).

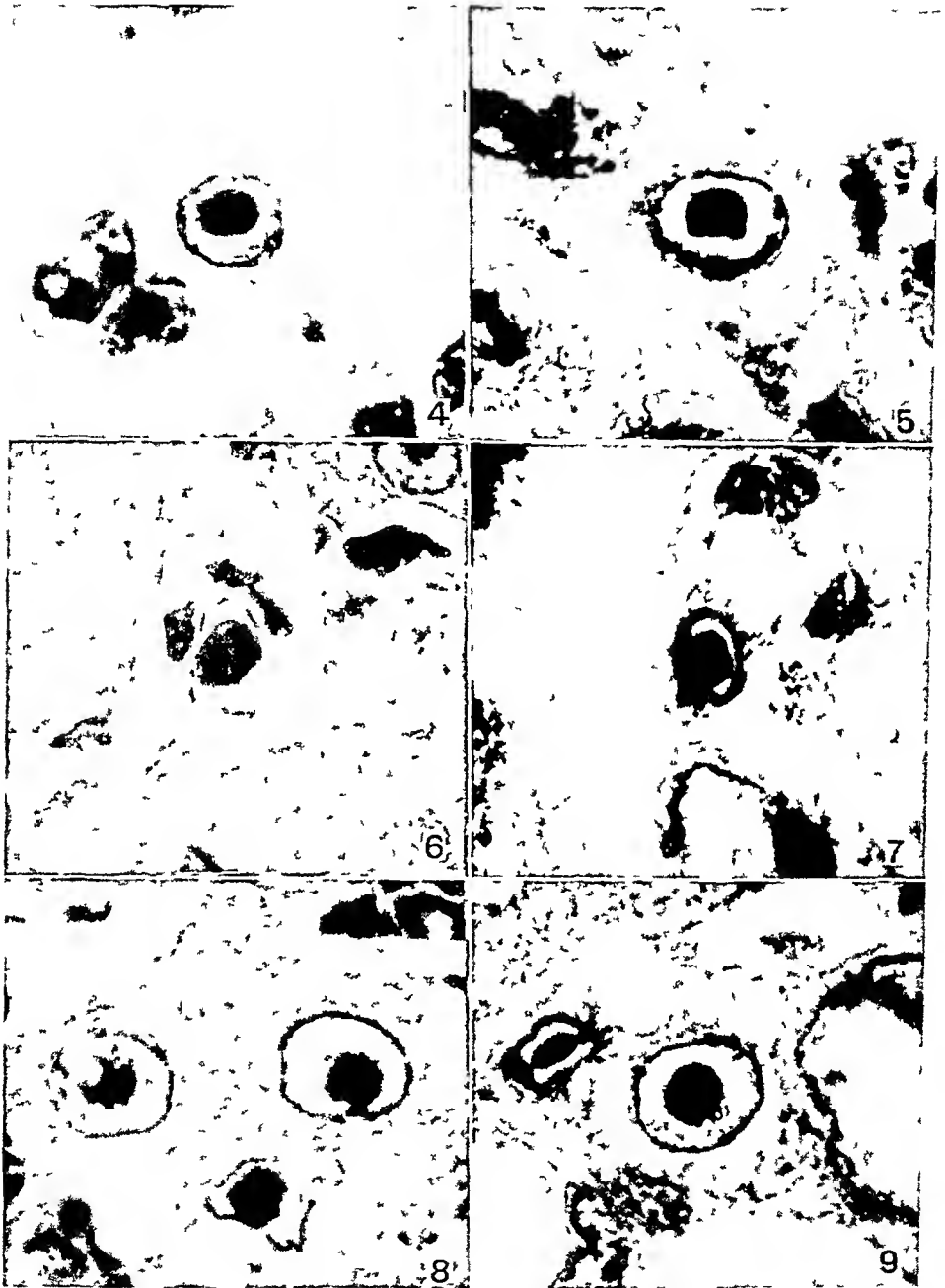


Fig 2—The three fields on the left are photomicrographs of intranuclear inclusions in the liver cells of dogs (nos 36 and 67), $\times 1,200$, those on the right are also photomicrographs but of inclusions caused by virus III in the testicles of rabbits taken at a higher magnification of 1,600 diameters. The similarity between the inclusions in dogs and those in the virus III infection is evident.

But when we came to the inclusions produced by virus III in the testicle, the correspondence was remarkably close. Figure 2 has been prepared in order that it may be accurately gaged. The fields are arranged in two columns. To the left are three photomicrographs (4, 6 and 8) of the questionable inclusions in the livers of dogs, while to the right are three other photomicrographs (5, 7 and 9) of the inclusions produced by virus III in the testicles of rabbits, which were unfortunately taken at a higher magnification, which as the figures are reproduced amounts to 1,600 diameters instead of 1,200. In this way, provision is made for three comparisons.

In the first pair, an inclusion is represented in the nucleus of a hepatic cell of a dog (4) and another in a cell inhabiting the interstitial tissue between the seminiferous tubules of the rabbit's testicle (5). It will be noted that the inclusions are of about the same size and approximately of the same density, though the virus III inclusion is a little darker in the photomicrograph. The clear area between the centrally placed inclusion and the nuclear membrane is less marked in the liver cell than in the other. There is a margination of chromatin on the nuclear membrane in both, but it is more extensive in the case of the nucleus injured by virus III.

The second pair of fields (i. e. 6 and 7) illustrates also a close degree of correspondence. Both represent intranuclear inclusions in endothelial cells. Here, again, the inclusion caused by virus III (7) appears to be rather more dense, but this, we think, is not significant. It may be due to differences in exposure and in printing in making the photomicrographs, for corresponding differences were not observed in the actual study of the specimens. The clear area between the inclusion and the nuclear membrane is relatively more extensive in the case of the unknown inclusion (6), and the margination of chromatin is less noticeable.

In the third and last pair of fields, namely, 8 and 9, several affected nuclei are represented, three in hepatic cells of the dog's liver and two in the rabbit's testicle. The smaller of these two is an endothelial nucleus and the larger is the nucleus of an interstitial cell. The similarity of the inclusions is obvious and does not require detailed mention.

If it were not for the fact that liver cells are involved in one instance and the cells of the testicle in the other, we believe that it would be impossible to distinguish between the inclusions. It may be added that the nuclear changes shown in a photomicrograph of Rivers and Tillett¹⁰ are likewise indistinguishable from those seen in our two dog livers.

¹⁰ Rivers, T. M., and Tillett, W. S. Further Observations on the Phenomena Encountered in Attempting to Transmit Varicella to Rabbits, *J. Exper. Med.* **39** 777 (fig. 2) 1924, The Lesions in Rabbits Experimentally Infected by a Virus Encountered in the Attempted Transmission of Varicella, *ibid.* **40** 281, 1924.

Having in mind the methods by which Rivers and Tillett concentrated and established virus III in the testicles of rabbits, we made corresponding experiments with dogs. They stated that it was only after four consecutive passages of ground up testicle substance that distinctive lesions were produced containing the intranuclear inclusions, and, further, that an interval of from three to six days was allowed to elapse after each intratesticular inoculation before the inoculated testicles were removed and ground up in saline solution for the inoculation next in series.

Accordingly, with aseptic precautions we removed a fragment of liver from an apparently normal dog and made from it a 10 per cent emulsion in physiologic solution of sodium chloride. A small opening was made in the abdominal wall of a second dog which was under ether anesthesia, and 10 cc of the emulsion was injected by a hypodermic syringe into the liver substance at a depth of about 1 cm from the surface in selected areas which could be accurately located again later, both to the right and to the left of the anterior median fissure. After four days had elapsed, during which the dog showed no untoward symptoms, tissue was removed from the sites of injection. Some of it was preserved for histologic examination, and the remainder was emulsified and passed to a third dog in the same manner. This third dog remained apparently normal. After four days, passage was made from the third to a fourth dog, which died twenty-four hours later from severe peritonitis and septicemia. The emulsion made from tissue from the areas of injection in this animal was consequently filtered through a Berkefeld N candle, and the filtrate was injected intrahepatically into a fifth dog. This fifth dog exhibited no resulting clinical symptoms and was chloroformed likewise on the fourth day. Unfiltered emulsion was then passed to a sixth dog, which also remained apparently normal. After the same period of four days, the hepatic emulsion made from its liver was injected intrahepatically into a seventh and an eighth dog, and a Berkefeld filtrate of the same emulsion was made and injected into the right testicles of two rabbits. The seventh dog was chloroformed after two days and the eighth dog after six days. Neither showed any intranuclear inclusions. Both rabbits were killed forty-eight hours after inoculation, and in their testicles also we failed to find any intranuclear inclusions. Inclusions were also absent in all of the intervening transfer animals. This means that our efforts by repeated passage to establish the virus, if any, responsible for the development of the inclusions were unsuccessful.

There is no known filtrable virus disease in dogs of which these inclusions, so closely resembling those of virus III, are likely to be the expression. The inclusions which have been described by many investigators in canine distemper are cytoplasmic and are generally restricted

to the cells of the central nervous system, though some have been reported by Babes and Starcovici¹¹ in the bronchial and alveolar epithelial cells as well. Orel and Silberstein¹² presented evidence that in a certain number of dogs a filtrable virus exists in the nasal passages, which on corneal, subdural and endolumbar inoculation causes death in both dogs and rabbits, but they said nothing of the occurrence of intranuclear inclusions. We have not as yet made a search for this virus.

COMMENT

It is improbable that the inclusions which we have described in the livers of these two dogs were merely the result of the histologic technic employed, because the same technic was used in the case of many other dogs without bringing them to light, and because repeated attempts by numerous workers to produce inclusions experimentally have failed. It is also unlikely that they resulted from the experiments performed by Dieckmann, for they have made their appearance in only two of the sixty-eight dogs examined, and also because we repeated the treatment accorded to these two dogs just as accurately as we could in the case of five others without producing any inclusions. Our series of dogs, which were not included in Dieckmann's experiments, is by comparison a small one, amounting to only sixteen, but in these no inclusions were seen. It is possible that if this series were extended to an equal number of animals, others showing intranuclear inclusions would be discovered.

The tendency now is to regard the presence of such inclusions as indicative of the action of a filtrable virus. Cole and Kuttner,¹³ for instance, espoused this interpretation definitely. After many attempts to produce intranuclear inclusions by other means than the injection of filtrable viruses had proved unsuccessful, they summed up by saying: "It is true that Luger and Lauda have mentioned the occurrence of similar structures in a case of salvarsan dermatitis. Even though these lesions should be present in isolated instances of this kind, it would be necessary to demonstrate the absence of a filterable virus in the given instance before the present conception of the direct relationship between these nuclear changes and filterable viruses would become untenable." In other words, these investigators believed that when typical intra-

11 Babes, V., and Starcovici, C. Sur les corpuscles particulieres trouves dans la maladie des jeunes chiens, *Compt rend Soc de biol* **73** 229, 1912.

12 Orel, H., and Silberstein, F. Experimentelle Encephalitisstudien. IV. Ueber das Vorkommen von Encephalitisvirus im Nasenrachenraum gesunder Hunde, *Ztschr f d ges exper Med* **44** 280, 1925.

13 Cole, R., and Kuttner, A. G. A Filterable Virus Present in the Submaxillary Glands of Guinea-Pigs, *J Exper Med* **44** 855, 1926.

nuclear inclusions are found, the presence of a filtrable virus is to be assumed, unless its absence can be proved experimentally

While we hesitate to subscribe without reservation to the point of view expressed by Cole and Kuttner, we do feel that our observation of intranuclear inclusions in these two dogs is on a par with the occasional discovery of intranuclear inclusions in a small percentage of human beings, particularly in infants, in the absence of distinctive clinical symptoms (Goodpasture and Talbot,¹⁴ Wilson and DuBois,¹⁵ Von Glahn and Pappenheimer¹⁶ and others) There is this difference, however, that the possibility of experimentation in dogs holds out greater hope for an understanding of the problem than the study of human tissues, which must always be largely opportunistic

CONCLUSION

Intranuclear inclusions were found abundantly in the hepatic cells and endothelial cells of two dogs in association with centrally placed necrotic changes in the lobules The further observation that these intranuclear inclusions are indistinguishable from the inclusions which are produced in the testicles of rabbits by the action of virus III indicates the possibility that a hitherto unrecognized filtrable virus may occur in a small percentage of these common laboratory animals

14 Goodpasture, E W, and Talbot, F B Concerning the Nature of "Protozoan-Like" Cells in Certain Lesions of Infancy, *Am J Dis Child* **21** 415 (May) 1921

15 Wilson, J R, and DuBois, R O Report of a Fatal Case of Keratomalacia in an Infant, with Postmortem Examination, *Am J Dis Child* **26** 431 (Nov) 1923

16 Von Glahn, W C, and Pappenheimer A M Intranuclear Inclusions in Visceral Disease, *Am J Path* **1** 445, 1925

THE EFFECT OF INTRAVENOUS INJECTION OF DEXTROSE ON THE KUPFFER CELLS OF THE LIVER^{*}

HARRY KOSTER, M D

M A GOLDZIEHER, M D

AND

W S COLLENS, M D

BROOKLYN

In the course of our studies on the value of injections of dextrose in the postoperative state, histologic examination of the liver was performed as a routine procedure. In a series of twenty-seven cases in which upper abdominal operations were done, the patients were subjected to excisions of two wedge-shaped pieces of liver. One section was removed immediately before and another half an hour after the intravenous administration of 250 cc of 20 per cent dextrose solution. Some of these patients received an injection of either 5 cc of a solution of trypan blue or 5 cc of Higgins' india ink into the left gastro-epiploic vein. These injections of dye were given for the purpose of vital staining the reticulo-endothelial cells of the liver in order more easily to visualize any possible change in them.

The order of the steps in our experiment can be summarized as follows. Under spinal anesthesia an upper right rectus incision was made. The dye for vital staining was then injected. The first excision of liver tissue followed. Immediately afterward dextrose was injected intravenously into a vein of the antecubital fossa. The operation was then performed, and half an hour after the injection of dextrose a second piece of liver was removed. The control experiment consisted of the substitution of 250 cc of physiologic solution of sodium chloride for dextrose. The sections of liver were fixed in formaldehyde, and frozen as well as paraffin sections were made. The sections were studied partly unstained and partly after application of the usual staining methods.

HISTOLOGIC DESCRIPTION

In normal human liver, if proper staining is employed, the nuclei of the Kupffer cells stand out fairly well because of their intense absorption of hematoxylin. It is true that in some of these cells the nuclei are larger and are only fairly stained. The majority, however, appear as elongated and more or less spindle-shaped or rod-shaped

^{*} Submitted for publication, Jan 10, 1930

^{*} From the Departments of Surgery and Pathology, Crown Heights Hospital

nuclei perfectly parallel to the capillary wall. After the injection of dextrose most of the nuclei change their appearance and become larger and oval and show a much less dense distribution of their chromatin. In consequence of these changes, the staining with hematoxylin is much lighter. These nuclear changes are accompanied by swelling of the cytoplasm, which seems to detach itself more from the capillary wall. It also seems that the cytoplasm of these cells, after the injection of dextrose, stains more intensely and assumes a somewhat bluish shade. This would indicate a certain basophilia of the cytoplasm, or a change in the pH toward the acid side.



Fig. 1—Section of the liver before the injection of dextrose. Note the dark rod-shaped nuclei of the Kupffer cells.

The changes described, although definite, are so minute that they might be overlooked by the less attentive observer. If, however, vital staining is employed previous to the injection of dextrose, the changes are much more conspicuous. While the faintly stained cytoplasm of the Kupffer cells is not easy to observe, the presence of trypan blue and particularly of india ink demonstrates strikingly the swelling of the cell bodies. These larger cells, however, seem to ingest more of the dye-stuff than they would take in before the administration of dextrose. In other words, it seems that they are more effective phagocytes after than before the injection of dextrose.

The histologic observations can be summarized as follows. The injection of dextrose elicits morphologic changes in the Kupffer cells

which consist of swelling of the cell body and nucleus, changes also occur in the chromatin distribution and in the staining properties of the cytoplasm. These changes are observed readily in the Kupffer cells without the vital staining. They were much more conspicuous when vital staining was employed, particularly in the cases in which india ink was used. But it also seems that the phagocytosis of the Kupffer cells for the dye is enhanced by the stimulation which the cell has apparently received by experimental procedure.

Swelling of a cell and its nucleus with concomitant changes in the chromatin distribution of the latter is looked on as an expression of



Fig 2—Section of the liver from the same patient after the injection of dextrose. Note the larger, paler nuclei and the swollen cytoplasm of the Kupffer cells at *A*.

increased function of that particular cell. The changes described in the Kupffer cells justify the opinion that they have been stimulated to increased activity. The stimulating factor is undoubtedly the dextrose solution. This has been ascertained by the control which includes cases in which injections of dextrose were made without previous vital staining and cases in which vital staining was employed but physiologic solution of sodium chloride substituted for dextrose. In the control experiments, these changes were observed in the former but not in the latter set. This would indicate definitely that the dextrose alone was responsible for the changes in the cells.

We realize that the changes produced by the injection of dextrose are not specific, they are similar to changes that occur after the injection of protein bodies, metal salts and hormones. In all of these instances, however, their significance is similar. They indicate increased functional activity. The Kupffer cells of the liver form part of the reticulo-endothelial system, the manifold function of which includes defense of the organism against infection and participation in intermediary metabolism. Stimulation of the reticulo-endothelial cells is expected to increase the resistance against infection and to facilitate the course of metabolic processes.



Fig. 3—Section of the liver stained vitally with india ink

The intravenous injection of dextrose has been found of considerable clinical value in many conditions. In the postoperative state complicated by infection or shock it is our experience that dextrose has a distinct value. It is helpful in overcoming the severity of the infection, it combats shock and favors smoother convalescence. Similar experiences are universally reported, and the administration of dextrose has become a generally accepted therapeutic procedure.

Schoenig,¹ in a study of the effect of massive doses of the roentgen rays in malignant conditions, demonstrated an inability on the part of the reticulo-endothelial cells to store vital dyes during the period of

1 Schoenig. *Klin Wchnschr* 8 651, 1929

1000 röntgen "shock" This disability of the cells was found in direct proportion to the severity of the clinical symptoms of "shock" Schoenberg believed that the injury to the reticulo-endothelial cells by irradiation resulted in their inability to dispose adequately of protein cleavage products which were formed by the 1000 röntgen exposure The value of intravenous injections of dextrose in the treatment for 1000 röntgen shock, as advised by Mayer² and others, could be ascribed to a stimulatory effect on the reticulo-endothelial cells as a result of which they could resume their physiologic functions and dispose of the toxic elements Such stimulation would be analogous to that shown in our experiments

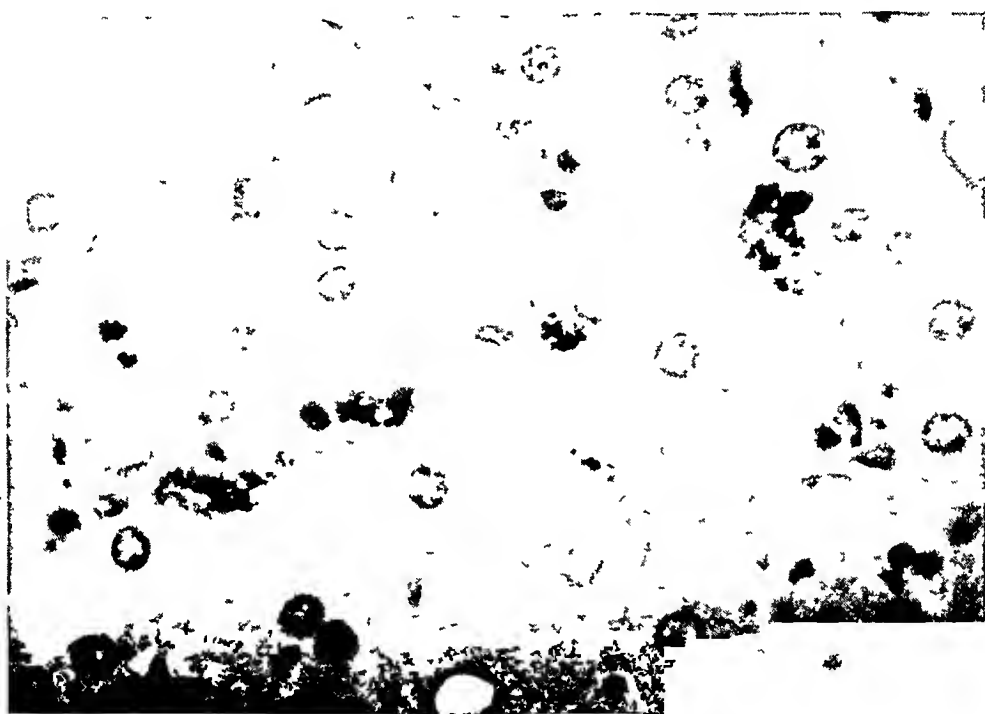


Fig 4—Section of the liver from the same patient as in figure 3, after the injection of dextrose Note the large detached Kupffer cells with the abundant store of India ink

In view of the tremendous amount of literature on the clinical value of the intravenous injection of dextrose, it seems surprising that so far no attempt has been made to determine scientifically the means by which it is of value to the body It seems to us that dextrose could be of value in only two ways (1) as a fuel and (2) as a stimulant of the defense mechanism Regarding the former, a subsequent paper will demonstrate the inability of the body to utilize as a fuel post-operatively intravenously injected dextrose Its value as a stimulus is demonstrated by our histologic observations

² Mayer, E. G., quoted by Muhlmann, E. *Strahlentherapie* 27: 307, 1928

CONCLUSIONS

The intravenous injection of dextrose elicits changes in the Kupffer cells. These changes are indicative of enhanced functional activity. The beneficial clinical effects of the intravenous injection of dextrose postoperatively are attributed to the stimulation of the reticulo-endothelial system.

NEGATIVE EFFECT OF LIVER EXTRACT ON RATE OF DIVISION OF THE RED BLOOD CELL IN CHICK BLASTODERMS*

GULLI LINDH MULLER, M D

BOSTON

In a preliminary report by Sabin, quoted by Cohn, Minot, Alles and Salter,¹ suggestive evidence was presented that liver extract effective in pernicious anemia increased the rate of division of the megaloblast in living chick embryo. She reported

In a series of 266 early blastoderms mounted in Locke solution, to which had been added chicken bouillon as prepared by Lewis and Lewis, no second division of the cells of a given blood island was observed in intervals of from 3 to 6 hours.² In three successive preparations in which extract (Preparation XL R) had been added to the medium a second cell division was seen. In two preparations the second division was of a blood island and the interval approximated three hours, in the third preparation the second division was of an endothelial cell, making the wall of the vessel, and the interval was approximately one hour. The preparations were fixed just as the second cell division was observed and they confirm the observation that the blood islands in the two preparations and the endothelium in the third were in a cycle of cell division. In all of these chicks the heart action remained very vigorous throughout the experiment, so that there was no sign of any toxic substance involved. This material is interesting inasmuch as the blood islands during the stages studied are made up entirely of the megaloblast.¹

This observation, if verified, would be of fundamental importance, because it might furnish a method urgently needed, for testing the potency of material effective in pernicious anemia, and it might also indicate the possible action on red blood cells of the principle effective in pernicious anemia.

The present study on the normal rate of division in the megaloblast was undertaken at the request of Dr. Sabin, to whom I am indebted for knowledge of the technic and for advice pertinent to such a study. Her preliminary observations as quoted have been verified, but no evi-

* Submitted for publication, Feb. 19, 1930.

* From the Thorndike Memorial Laboratory, Boston City Hospital.

1 Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T. The Nature of the Material in Liver Effective in Pernicious Anemia. *J. Biol. Chem.* **77**, 325, 1928.

2 Sabin, F. R. Studies on the Origin of Blood Vessels, and of Red Blood Corpuscles as Seen in the Living Blastoderm of Chicks During the Second Day of Incubation, *Contrib. Embryol., Carnegie Institution, Washington, D. C.*, **9**, 213, 1920.

dence has been obtained that liver extract promotes the rate of division of the megaloblast in the chick embryo. The misconception was due to the fact that Dr. Sabin did not have opportunity to make adequate control observations on the normal rate of division of the young red blood cell in the living chick embryo.

METHODS AND PROCEDURE

The preparation of the chick embryo and the solutions used were essentially the same, with minor modifications, as those described by Sabin in her excellent monograph on the origin of blood vessels and of red blood corpuscles in the blastoderm.² The preparation of the Locke-Lewis solution was modified to prevent a tendency toward the formation of a precipitate when the solution was sterilized in the autoclave. Satisfactory results were obtained by autoclaving each ingredient separately and, after cooling, mixing them in proper proportions under sterile precautions, then transferring 10 cc. into sterile test tubes. The Locke-Lewis solution thus prepared was kept in the icebox, and bacterial contaminations were not encountered, as shown by frequent tests for bacterial growth. This modification of the preparation of the Locke-Lewis solution obviated daily mixing and sterilization, in spite of which precipitation in the solution could not always be avoided.

OBSERVATIONS

The living chick blastoderm was studied for a variable length of time, usually until the second cell division in a blood island had been observed. The criteria for division of the red blood cells have been admirably described by Sabin for chick embryos. Thus, in the resting stage, the young blood island shows no definite cell outlines but looks like a homogeneous, somewhat glandular mass, often with a definite border. After an interval of time, the mass becomes refractive, the cell outlines become distinct, and mitotic figures can be observed. The actual cell division then occurs. This final process may be rapid and is often not noticed unless attention is directed constantly to certain cells in a given area. After cell division has occurred, the cells lose their refractivity, cell outlines and individuality, and become dull looking and indistinct. Photographs and drawings of the blood islands during various stages of cell division appear in Sabin's monograph.² In no instance was crenation of the red blood cells or laking of the hemoglobin detected.

In the present study, the attention was focused, as a rule, on a few cells, and cell division was looked for when possible, in the same cells, while in addition the general cycles of cell division were observed. The observations on the division of cells in the living chick embryo were verified in fixed and stained preparations. In many instances the preparation was not fixed until the actual division had taken place while others were fixed when many mitotic figures were present.

The intervals of time between the cell divisions of the red blood cells in apparently normal chick embryos and explanatory data are

set forth in the table. The table is arranged according to the length of time observed between the first and the second cell division. The first cell division after mounting occurred within one-half hour in twenty-nine of the forty-six preparations studied and recorded. This fact suggests that perhaps the mechanical stimulation of washing and mounting the embryo may have some influence in hastening the process of cell division.

The Rate of Division of the Megaloblast in the Normal Chick Embryo

Preparation*	Time of Incubation		Interval Between Mounting and First Cell Division, Minutes	Interval Between First and Second Cell Division, Minutes	Number of Somites at Time of Fixation	Remarks
	Hours	Minutes				
13 B	48	40	25	45	25	Single cell island
4 B	48	50	10	60	20	Single cell island
15 B	48	00	30	60	21	Small cell island
15 A	49	55	5	60	19	
16 B	48	10	25	65	10	Small cell island
23 B	52	30	25	70	17	Large cell island
17 A	50	18	20	70	21	Small cell island
46 A	47	40	15	75		Small cell island
12 B	49	20	50	80	19	Small cell island
22 B	49	30	5	80		Medium sized cell island
8 B	47	25	25	85	16	Small cell island
5 B	69	20	30	85		Small cell island
10 B	48	25	40	90	20	Small cell island
24 B	17	30	65	90	10	Small cell island
47 A	47	45	60	90	24	Single cell island
48 A	47	55	40	90	21	Small cell island
2 B	48	15	50	95	20	Medium sized cell island
8 A	47	00	30	100	20	Medium sized cell island
75 A	51	15	110	100	21	Large cell island
211 A	17	30	15	100	24	Large cell island
212 A	47	15	30	100	25	Large cell island
1 B	46	45	50	105	18	Large cell island
18 A	48	40	20	105	16	Medium sized cell island
32 B	48	20	30	110	11	Small cell island
28 B	49	00	20	115	19	Medium-sized cell island
7 A	50	35	35	115	21	Small cell island
73 A	17	55	20	115	21	Medium sized cell island
241 A	46	30	55	115		Medium sized cell island
26 B	48	00	10	120	17	Small cell island
221 A	43	15	40	120	20	Large cell island
13 A	46	45	25	130	23	Large cell island
225 A	45	55	30	130	22	Small cell island
95 A	46	05	30	135	18	Small cell island
240 A	45	30	60	140		Medium sized cell island
35 B	49	35	20	145	21	Small cell island
22 A	50	00	30	150	21	Medium sized cell island
73 A	48	15	60	170	17	Large cell island
19 A	19	20	25	180	19	Large cell island
9 B	68	15	100		29	Small cell island
21 B	50	10	110		18	Large cell island
33 B	51	45	10		10	Medium sized cell island
39 B	48	25	10		23	Small cell island nuclei distinct
12 A	49	10	110		16	Medium sized cell island
56 A	44	45	45		18	Large cell island
74 A	48	50	20		18	Large cell island

* "A" after the number of the preparation refers to a series done between May and August, while "B" designates a series during the months of March and April.

From an examination of this table in which the figures of time have been expressed in the nearest round number it may be seen that the interval of time between the first and the second cell division in thirty-nine preparations of living chick embryo varied between forty-five minutes and three hours. The age of the blastoderm when mounted was

usually approximately 48 hours but varied from 43 to 69 hours. In four preparations studied long enough for a second cell division to occur none was observed.

A correlation was made between the size of the group of cells observed and the interval of time between cell divisions. In a general way the interval between two cell divisions was shorter in the case of single cells or small islands, although an absolute correlation cannot be made out. A considerable variation occurred also in the size of embryos of the same age, as is indicated by the total number of somites.

The interval of time between the cell divisions of young red blood cells in eight chick embryos mounted in Locke-Lewis solution and the identical liver extract (preparation XLR) used by Dr. Sabin was found to be between 80 and 130 minutes. Dr. Edwin J. Cohn supplied the liver extract.

It is thus evident that although the observations of Sabin on the rate of division of the megaloblast in the chick embryo mounted in Locke-Lewis solution and the identical liver extract in the same dilution were confirmed, this rate of cell division does not seem to differ from that of the normal cell division of megaloblasts of blastoderms mounted in Locke-Lewis solution only. Consequently this procedure gives no information concerning the potency of liver extracts, nor can any conclusions be drawn from such observations as to the influence on the megaloblast of the active principle effective in pernicious anemia. From the observations described no evidence has been obtained to suggest that an increased rate of cell division occurs in young red blood cells of the chick subjected to the direct influence of liver extracts potent in pernicious anemia.

CONCLUSIONS

The interval of time between cell divisions in young red blood cells in the normal blastoderm varied from forty-five minutes to three hours. The rate of division was apparently not influenced when liver extract effective in pernicious anemia was added to the mounting fluid.

TERATOMA AND TERATOID TUMORS OF THE BRAIN ^k

KIYOSHI HOSOI, M D

Senior Eugene Littauer Research Fellow in Pathology, Albany Medical College
ALBANY, N Y

Intracranial new growths of bidermal or tridermal origin are among the rarest of tumors. There is no mention of a teratoma in the 99 case reports compiled by White¹ from the records of Guy's Hospital for the years from 1872 to 1884. Frankl-Hochwart² in 1909 found only 2 cases of teratoma, or 2.1 per cent, among 97 collected cases of hypophyseal tumors. In Cushing's³ list of 868 verified intracranial tumors, there were 4, or 0.5 per cent. Since 1916, few cases have been reported. The pituitary and the pineal glands seem to be the sites of predilection for these teratoids and teratomas. The case here reported is unique in that the teratoma apparently arose from the cerebellum. Dr W. M. Baldwin of the department of anatomy of Albany Medical College, to whom the brain was originally submitted, permitted me to study the specimen.

REPORT OF A CASE

History—W. M., a white man, aged 27, was admitted in 1918 to the service of Dr. Charles Bernstein, Rome State School (Rome, N. Y.), an institution for mental defectives. His mental peculiarity was first noticed when he was an infant. He had never been able to walk. He first talked when 3 years old and in school was able to reach the second grade. He was obedient, industrious but inadequate, considerate, sensitive, affectionate, adaptable and clean.

His father, an inmate of the Brunswick Home, had Huntington's chorea. His mother died at the age of 51 years from "brain abscess," after being ill for three months. Four brothers and four sisters were living and in good health.

Physical Examination—Physical examination showed a hydrocephalic dwarf, 4 feet (122 cm.) in height, with kyphosis and right lateral curvature of the spine. The jaw was of the prognathous type, and the forehead was high and bulging. The anteroposterior diameter of the head measured 24 cm., the anteroposterior

* Submitted for publication, Feb. 11, 1930.

^k From the Department of Pathology, Albany Medical College, and the Pathological Laboratory of the Albany Hospital.

1 White, W. H. One Hundred Cases of Cerebral Tumor with Reference to Cause, Operative Treatment, Mode of Death and General Symptoms, Guy's Hosp. Rep. **43** 117, 1886.

2 Frankl-Hochwart, L. von. Die Diagnostik der Hypophysistumoren ohne Akromegalie, Wien med. Wchnschr. **59** 2326, 1909.

3 Cushing, H. Notes on a Series of Intracranial Tumors and Conditions Simulating Them, Tumor Suspects, Tumors Unverified, Tumors Verified, Arch. Neurol. & Psychiat. **10** 605 (Dec.) 1923.

curve 45 cm, the binauricular curve 40 cm, the maximum transverse diameter 19.5 cm, and the greatest circumference 70 cm, giving a cranial capacity of 1,364 cc and a cephalic index of 0.81. The bridge of his nose was low, the palate high and broad. An excess of hair was present over the body. The patient was poorly developed but well nourished, the muscles were flabby, the skin was smooth and moist.

The chest showed poor development, the amount of chest expansion was only 1 inch (2.5 cm). The point of maximum cardiac intensity was in the fourth interspace, the right border of the heart was 1 cm to the right of the midsternal line, the left border, 10 cm to the left of the midsternal line. The heart sounds were muffled, but regular. The blood pressure was 108 systolic and 80 diastolic. The abdomen was not remarkable. The lower extremities were shrunken and useless.



Fig 1—Drawing of right mesial aspect of brain. The location of the cerebellar tumor and its general relationship to surrounding structures are clearly shown. Note the enormous communication between the lateral ventricles.

The pupils were equal and regular. Sight was good. The patient was able to hear the ticking of a watch held 2 feet (60.9 cm) from each ear. He distinguished between the odors of lemon, cinnamon and peppermint. He differentiated between sour, sweet and bitter. His speech was normal. The pain, touch and stereognostic senses were normal. The corneal, pharyngeal, umbilical, plantar, elbow, wrist, supinator and bicipital reflexes were all positive. The knee reflexes were exaggerated. The tongue protruded straight. The strength of his grip was 40 pounds (18.1 Kg) for the right and left hands.

The Wassermann test of the blood was negative. The hemoglobin was 80 per cent, with a polymorphonuclear differential count of 74 per cent.

The results of the Binet-Simon test were as follows. The patient was extremely nervous, talked plainly and seemed rather bright. He was handicapped

in not being able to read readily, but appeared intelligent otherwise. He was able to cooperate and concentrate well and had clean habits. His mental age was calculated at 8 years and 4 months when his physical age was 27 years, and later at 10 years when his physical age was 29, in other words, he had definite feeble-mindedness of the moron type.

During his five years' stay at the State School, he had parotitis, diphtheria and measles. At various times, he complained of severe headaches with vomiting, and of pains in the stomach and in the back, and he had subnormal temperatures of 96.4 F. In 1923, he developed influenza with a terminal fatal bronchopneumonia.



Fig. 2—Photomicrograph of a section of the tumor with two large cysts lined by stratified squamous epithelium. It shows hair follicles, sebaceous glands and fatty tissue. The cerebellar leaf at the extreme left indicates the intimate relationship between it and the tumor tissues. Hematoxylin and eosin stains, $\times 31$.

Necropsy—The necropsy was limited to the head. The brain was examined after fixation in a dilute solution of formaldehyde, U. S. P. (1:10). The dura mater was of the thinness of paper and remarkably transparent like a thin sheet of celluloid wrapped around the brain. The sulci were everywhere shallow, being mere depressions. The convolutions were plateau-like and broad, and averaged 19 mm in width. The brain with the dura weighed 1,358 Gm. The occipitofrontal diameter measured 20.3 cm, the bitemporal diameter 17 cm and the sagittal

diameter at about the level of the fissure of Rolando 13.5 cm. The lateral ventricles were enormously dilated the brain being 4 mm thick at the vertex, 14 mm thick at the frontal pole and 30 mm thick at the occipital pole. By actual measurement, the total capacity of both lateral ventricles was 1,070 cc. The third ventricle was dilated from side to side, so that the massa intermedia was stretched out into a slender cord 22 mm long with a diameter of 1 mm. In fact, it appeared as if the third ventricle were but a loculus of the greatly distended lateral ventricles. The foramen of Monro had been converted into an enormous communicating channel. The triangular fourth ventricle measured 2 cm. at the



Fig 3—Photomicrograph of a section of the tumor to show true bone formation with lacunae, haversian canals and marrow spaces. Nearby there are two cysts lined by squamous epithelium, and a sebaceous gland. Hematoxylin and eosin stains, $\times 31$.

base and 1 cm. in height. The caudal portions of the fourth ventricle were pressed together by a cystic tumor, originating in the inferior cerebellum and occupying the area of the cisterna magna, which had become obliterated (fig 1). This tumor completely blocked the exit of the cerebrospinal pathway, producing a massive internal hydrocephalus. The growth measured 3 by 3.5 by 2.8 cm. It was covered by a thin shell of cerebellar tissue, except where it abutted on the roof of the fourth ventricle in apposition to the tela choroidea. On sagittal section the cyst wall consisted of a thin fibrous layer, less than 1 mm. thick. How-

ever, the thicker portions lay in the white matter of the cerebellum, from which there was no definite delimitation of the tumor tissue. Indeed, here a bony nodule, 4 mm in its widest dimensions, and numerous hairs seemed to be embedded in the cerebellar substance itself. The contents of the larger cystic mass consisted of strands of light brown hair and degenerating cellular debris. There were several other minute cystic spaces. In addition islands of fatty tissue could be recognized grossly. The pineal and pituitary glands were not remarkable.

Microscopic Observations—Before staining, all the sections were first mordanted over night in potassium dichromate solution. Besides the routine stains

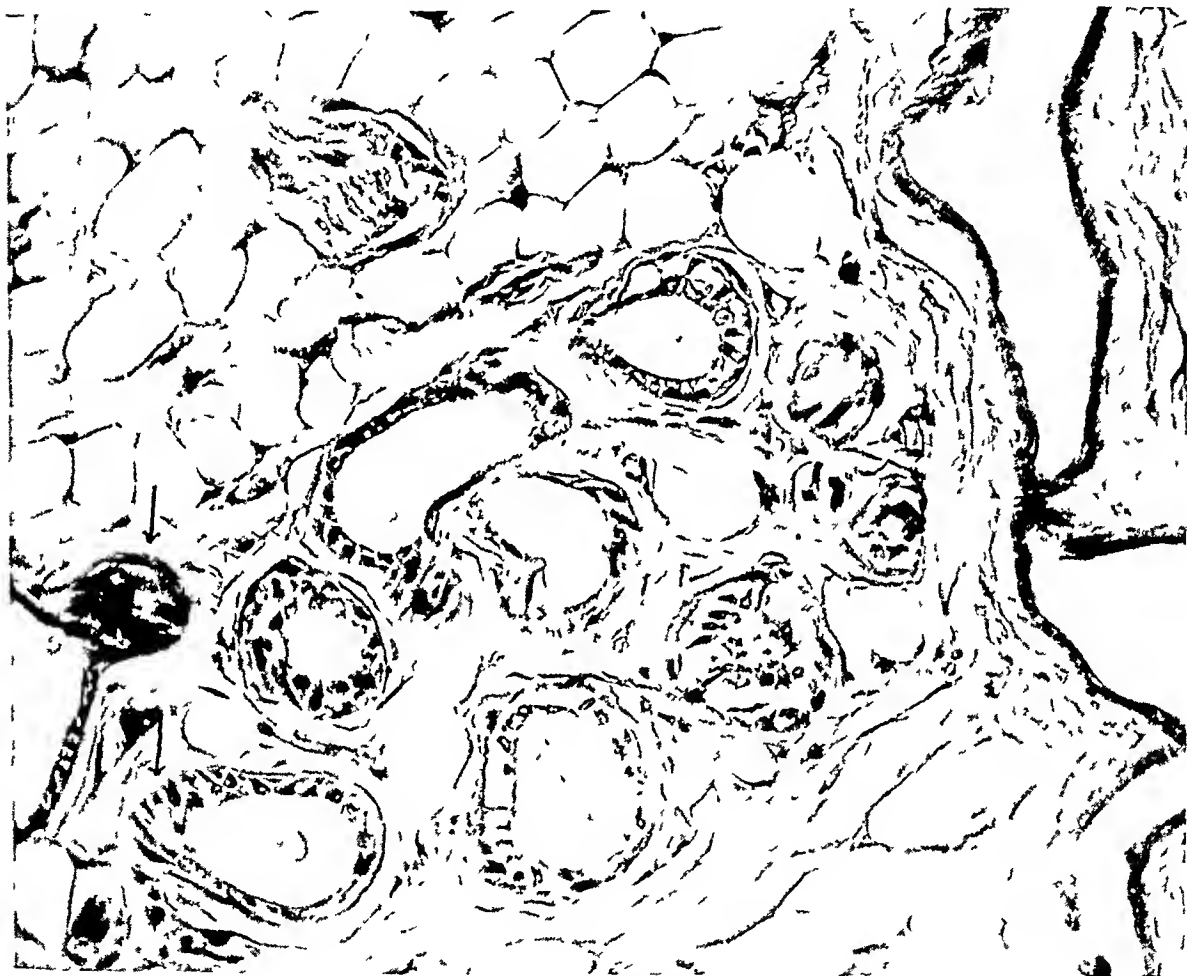


Fig 4—Photomicrograph of the fatty portion of the tumor to show the goblet cells lining the tubules, which contain a mucoid secretion. The arrows point to tubules cut obliquely, showing the outer single layer of smooth muscle cells. To the right, there are two large veins. Near the upper left hand corner is an obliquely cut strand of nerve fibers. Hematoxylin and eosin stains, $\times 265$.

with hematoxylin and eosin, I used van Gieson's picric acid-fuchsin, Mallory's phosphotungstic acid-hematoxylin, Weigert's resorcin-fuchsin, Foot and Menard's silver carbonate method⁴ and Penfield's combined method⁵.

⁴ Foot, N. C., and Menard, M. C. A Rapid Method for the Impregnation of Reticulum, *Arch. Path.* 4:211 (Aug.) 1927.

⁵ Penfield, W. A Method of Staining Oligodendroglia and Microglia, *Am. J. Path.* 4:153, 1928.

TABLE 1—Summary of Observations on Recorded Teratomas

No	Author	Sex	Age	Location of Tumor	Size of Tumor	Fetodermal Structures	Mesodermal Structures	Endodermal Structures
1	Coats Jr Path Soc London 38 14, 1886	M	13 years	Pineal	1½ by 1½ by 1¼ in (47 by 230 by 31 mm)	Epithelial pearls (?)	Cutilage, smooth muscle and spindle cell sarcoma	Goblet cells
2	Gauderer Zur Oculistik der Zuheldruesentumoren (Teratom der Glandulae pineales) Inaug-Dissertation, Gressen, 1889	M	12 years	Pineal	3.5 by 2.5 by 2.5 cm	Squamous cells and sweat glands (?)	Connective tissue, smooth muscle, cartilage, bone, osteoid tissue and fat	Goblet cells
3	Silver Beitr z path Anat u z allg Path 20 393, 1896	F	7 weeks	Third ventricle	8 by 10 by 12 mm	Fetal brain tissue, embryonal choroid plexus, squamous epithelium, embryonal eye (?), nerves and ganglion cells	Embryonal connective tissue, striated and smooth muscles, cartilage, bone and fetal blood islands (?)	Goblet cells and embryonal choroid
4	Gutzzeit In Teratom der Zirbeldruese. Inaug Dissertation, Koenigsberg, 1896	M	7½ years	Pineal	4 by 3.25 cm	Squamous epithelium, sweat glands and hair follicles	Very cellular connective tissue striated and smooth muscles, fat cells and cartilage	Goblet cells
5	Kon Beitr z path Anat u z allg Path 44 233 1908	M	37 years	Pituitary region	Haselnut	Squamous epithelium, appendicular cells, nerve fibers and fat tissue	Connective tissue, cartilage and bone	Chordal like tissue
6	Frankl-Hochwart Deutsche Zeitschr f Nervenhe 57 154, 1909	M	5½ years	Pineal	5 by 2.5 by 2.9 cm	Epidermis	Embryonal cartilage with ossification and stromal suggestive of spindle cell sarcoma	Goblet cells
7	Fukuo Ueber die Teratome der Glandula pinealis, Inaug. Dissertation, Muench, 1914	M	19 years	Pineal	Walshnut	Squamous epithelium sweat glands and hairs	Connective tissue striated and smooth muscles, cartilage, fat, bone with meloid tissue in marrow and osteoid tissue	Goblet cells
8	Schmincke Muenchen med Wchnschr 61 2043, 1914	M	19 years	Pineal	Walshnut	Thick gum like mass said to be represented		

9	Schmuneke	M	22 years	Pineal	Walshnut	Neuro-epithelium and ganglion cells	Connective tissue	High mucous forming cylindrical cells
10	Odeumatt Zur Diagnostik der Zirkeldruesentumoren, Inaug Dissertation, Zurich, 1915	M	10 years	Pineal	3 by 2 4 by 2 7 cm	Squamous epithelium	Cellular connective tissue, smooth muscle and cartilage	Goblet cells
11	Burton J Cancer Research 1 31, 1916	M	19 years	Pineal	4 2 by 3 by 4 4 cm	Squamous epithelium, salivary glands (?), hair follicles (?) and ganglion cells (?)	Connective tissue, striated and smooth muscles, cartilage and bone	Goblet cells
12	Bosco Proc P in Am Sc Cong, Washington, 1917, vol 10, pp 522-523	M	30 years	Region of tuber cinereum	4 by 2 by 3 cm	Hornified epithelium	Connective tissue and fat	Chorda tissue
13	Boehm Frankfurt Ztschr f Path 22 121, 1919	M	9 1/4 years	Pineal	5 cm in diameter	Squamous epithelium, embryonal teeth, ependymal rosettes, glia and young ganglion cells	Connective tissue, smooth muscle, cartilage and lymph follicles (?)	Goblet cells and respiratory tract epithelium
14	Frank Berl klin Wchnschr 57 888, 1920	M	20 years	Pineal	3 4 by 2 3 by 2 3 mm	Hornified squamous epithelium and glia	Connective tissue, smooth muscle and cartilage	Intestinal and respiratory tract epithelium
15	Luce Deutsche Ztschr f Nerven 68 69 187, 1921	F	5 1/2 years	Pineal	Large plum	All three germ layers said to be represented		
16	Klaproth Centralbl f allg Path u path Anat 32 617, 1922	M	15 1/2 years	Pineal	Small apple	Squamous epithelium, embryonic medullary tube, sebaceous glands and hairs	Connective tissue, smooth muscle and bone with myeloid tissue in marrow	Goblet cells
17	Derman Vuchows Arch f path Anat 259 767, 1926	?	1 month	Choroid plexus	Child's fist	Epidermis, pigmented epithelium, embryonal choroid plexus (?) and glia (?)	Connective tissue, striated muscle, cartilage, bone and fat	Goblet cells
18	Hosoi	M	27 years	Cerebellum	3 by 3 5 by 2 8 cm	Squamous epithelium, sebaceous glands, sweat glands (?), hair follicles and nerve fibers	Connective tissue, smooth muscle, bone with marrow and fat	Goblet cells

TABLE 2—*Summary of Observations on Recorded Teratoid Tumors*

No	Author	Sex	Age	Location of tumor	Size of tumor	Epithelial Structures	Mesodermal Structures	Structures Hand to Evaluate
1	Mayer Virchow's Arch f path Anat 20 536, 1861	M	10 weeks	Left cere bral hemi sphere	Apple	Epithelium sebaceous glands and hair	Connective tissue with malignant changes, cartilage and bone	
2	Weigert Virchow's Arch f path Anat 65 212, 1875	M	14 years	Pineal	3.5 by 3.5 by 3 cm	Epidermis, sebaceous glands, hair follicles and nerve fibers	Connective tissue, smooth muscle, cartilage and fat	Cysts lined with evendrie epi thelium
3	Filkson Virchow's Arch f path Anat 77 530, 1879	M	16 years	Pineal or choroid plexus (?)	5.8 by 1.7 by .3 cm	Pendyma and telio choroid (?)	Spindle cell sarcoma and cartilage	
4	Beck Ztschr f Heilk 4 303, 1853	F	74 years	Pituitary	2.5 by 2.7 by 2.4 cm	Fourteen teeth	Myomatous tissue, cartilage and bone	Cysts lined with ciliated epithelium
5	Simsbury Tr Path Soc Lond 17 57, 1886			Base of brain	Walnut	Epidermis	Connective tissue and fat cells	Numerous round cells
6	Strassmann and Streeker Virchow's Arch f path Anat 108 351, 1887	M	3 years	Choroid plexus	Walnut	Epithelium nervous and tubular glands, ganglion cells, cells and nerves	Connective tissue situated and smooth muscle, cartilage, bone, fat and lymphatic tissue	Cysts lined with one layered to several layered epithelium, ciliated epithelium
7	Tibeth Virchow's Arch f path Anat 17 71, 1898	F	75 years	Intra spinal nerve of thorax	Split pea	Nerves	Muscle, fat and lymphoid tissue	
8	Benda Beil med Wehnseh 7 1205, 1900	M	38 years	Pituitary	Walnut	Squamous epithelium	Connective tissue and bone	
9	Neumann Fin nepe Fall von Teratom der Zuheldruse, Inaug Dissertation, Koenigsberg, 1900	M	27 years	Pineal	1 by 3.25 cm	Squamous epithelium	Connective tissue, striated and smooth muscles, cartilage, fat and lymphoid tissue	Glands lined by endobial to high columnar epithelium
10	Ross Rev Neurol & Psychiat 4 389, 1906	M	77 years	Frontal lobe	1 inch (2.5 cm) in diameter	Epithelium	Fibrous tissue and fat	
11	Ross	M	75 years	Frontal lobe	Hen's egg	Skin, sebaceous glands and hairs	Plastic tissue, muscle, fat, embryonic blood vessels, cartilage and bone	

No.	Biography and Skull-rus. Un- cious Arch. f path Anat	F	Age	Pituitary	Size in diameter	Epithelium and glands	Connective tissue and bone
12	Biegman and Steinhilber, Neurol & Psychiat 189, 360, 1907						
13	Hecht J A M A 53: 1001 (Sept 25) 1909	F	11 years	Pituitary	¾ by 1 inch (1.9 by 2.5 cm)	Epithelium and salivary glands (?)	Embryonal connective tissue and giant cells
14	Bailey and Jelliffe Arch Int Med 8: 851 (Dec) 1911	M	12 years	Pineal	1.5 inches (3.75 cm) in diameter	Sebaceous material and hairs	Cartilage
15	Cushing The Pituitary Body and Its Disorders, Philadelphia, J B Lippincott Company, 1912	F	16 years	Pituitary	Golf ball		Myomatous tissue, cartilage and bone
16	Cushing	M	35 years	Pituitary	5 cm in diameter		Myomatous tissue, embryonic cartilage and few bone cells
17	Van den Bergh and Van Hasselt Nederl tijdschr v geneesk 1: 1271, 1913	M	8 years	Pineal	Small marble	Squamous epithelium, sebaceous glands, hairs and nerve tissue	Connective tissue, cartilage and bone
18	Brunnerster Bull Johns Hop kins Hosp 26: 410, 1915	M	60 years	Choroid plexus	4.7 by 2.5 by 3.5 cm	Multilayered epithelium and epithelium	Hyaline cartilage and bluish strands
19	Kato Tabib f Psychiat 15: 43, 1914	F	16 years	Cerebellar pontile angle	Pigeon egg	Hornified epithelium and ganglion cells	Connective tissue, muscle, fat and bone
20	Shtromovits Neurol Centr bl 17: 784, 1918	M	32 years	Cerebellum	Man's fist	Gland tissue (?) and hairs	Bone and fat
21	Globus Arch Neurol & Psychiat 9: 417 (April) 1923	F	6 years	Pituitary	4 by 3.5 cm	Squamous epithelium, salivary glands (?) and sebaceous glands (?)	Mucoid connective tissue, embryonal cartilage and bone with marrow
22	Hornik and Bailey Arch Neurol & Psychiat 11: 423 (April) 1925	M	3 years	Pineal		Horny epithelium, sebaceous glands and hairs	Cartilage, bone and fat
23	Klaus Nichols Arch f path Anat 27: 1546, 1929	F	Premature	Pituitary region	37 by 30 mm	Neuro epithelial tubules, glia, choroid plexus and embryonal eye (?)	Embryonal connective tissue, striated muscle (?), cartilage and bone

The large cyst and the smaller cystic spaces were all lined by stratified squamous epithelium. Beneath this epithelium, there were islands of well developed sebaceous glands and hair follicles (fig 2). A few rudimentary tubular sweat glands were present in one location near an epithelial cyst. These cysts contained necrotic cellular debris. Cholesterol crystals were present here and there in the more fibrous connective tissue matrix, which consisted mostly of collagen with a few elastic fibrils, as shown by van Gieson's and Weigert's stains. Elastic fibrils, however, were found most abundantly in the loose connective tissue layer just beneath the squamous lining of the various cysts. Several of the sections showed true bone formation with typical lacunae and haversian canals (fig 3). A few strands of smooth muscle cells could be identified, which stained yellow by van Gieson's method. There were many small spaces lined by cells, varying from cuboidal to columnar, which were difficult to identify. In one group of tubules lying in an island of fat, the lining cells were of the typical goblet cell type (fig 4). Each tubule was surrounded by a single layer of smooth muscle cells (stained yellow by van Gieson's method), which ran parallel with the lumen of the tubule best seen when the sections were cut obliquely or at a tangent to these tubules. This association of goblet cells and smooth muscle strongly indicated a derivation from the intestinal anlage. Large areas of fatty tissue were present. Blood vessels and small bundles of myelinated nerves were seen throughout the various sections. Fine strands of reticulum were demonstrable by the Foot and Menard silver stain in the loose connective tissue stroma, in the fatty tissue and in the walls of blood vessels.

In those areas near the periphery of the tumor in which there was an admixture of teratomatous structures and cerebellar tissue, the increase in neuroglia fibrillae was prominent, as shown by Mallory's phosphotungstic acid-hematoxylin. There was also a marked reactive gliosis in the sections from the brain stem, but only a moderate one in the cerebral cortex. In the sections of the cerebellum and cortex stained by the Penfield method, microglia and oligodendroglia were not significantly altered. The cortical ganglion cells and capillaries appeared much increased in number. This increase may have been only apparent, since the cortex had been markedly thinned by pressure from the internal hydrocephalus. The ganglion cells were well supplied with chromidial substances which showed no microscopic evidence of chromatolysis.

COMMENT

From table 1, it is seen that tridermal tumors or genuine teratomas of the brain are extremely rare. I have been able to find reports of 17 instances in the literature in 2 of which no detailed microscopic observations were given. On the other hand, teratoid tumors, though rare, occur more often, 23 such cases being recorded. Owing to the varying degrees of complexity and to the frequently undifferentiated character of these types of tumors, it is difficult to evaluate and classify many of the structures found in teratomatous and teratoid growths. From a study of the literature, it is seen that many do not differentiate between genuine teratomas and teratoid tumors. Yet one must take into consideration that a tumor which at one examination is obviously monodermal, owing to a marked overgrowth and proliferation of the derivatives of one germ layer at the expense of the other two primitive

layers, may have been tidermal in the beginning Askanazy⁶ considered his case of primary pineal chorio-epithelioma to be teratomatous, which makes this tumor an ectodermal derivative Goldzieher,⁷ on the other hand, interpreted his similar case as an angioblastic sarcoma, hence mesodermal in origin Ewing⁸ stated that a partially choriomatous structure is produced in testicular tumors by alterations in the cylindric cell lining of blood spaces, that smooth and striated muscles are occasional elements of the normal epiphysis, that ependymal epithelium may become high and cylindric or flat and squamous and that all the elements of these complex tumors, except dermal structures, may be derived from the pineal gland itself However, he believed that misplaced tissue may rest in the pineal and pituitary glands White's⁹ case of ganglioneuroma and Pappenheimer's¹⁰ case of neurogliome ependymale of the pineal gland showed the presence of muscle fibers, but as has been pointed out by Ewing and by Pappenheimer himself, one is not justified in calling these tumors bidermal because of this The data furnished by Bowlby,¹¹ Ogle¹² and de Monchy¹³ are meager and somewhat uncertain Takeya's¹⁴ and Kishenski and Tisenhausen's¹⁵ articles are inaccessible Schmincke and Luce merely mentioned that derivatives of all three germ layers were found in their cases, and Hueter¹⁶ that microscopically the pineal tumor was a tera-

6 Askanazy, M Teratom und Chorioepitheliom der Zirbel, Verhandl Deutsche path Gesellsch **10** 58, 1906

7 Goldzieher, M Ueber eine Zirbeldruesengeschwulst, Virchows Arch f path Anat **213-214** 353, 1913

8 Ewing, J Neoplastic Diseases, ed 2, Philadelphia, W B Saunders Company, 1922, p 949

9 White, W H A Myo-Neuroma of the Pituitary Body, Tr Path Soc London **36** 37, 1885

10 Pappenheimer, A M Ueber Geschwulste des Corpus pineale, Virchows Arch f path Anat **200** 122, 1910

11 Bowlby, A A Tumor of the Pituitary Body, Tr Path Soc London **36** 35, 1885

12 Ogle, C (1) Sarcoma of the Pineal Body with Diffuse Melanotic Sarcoma of the Surface of the Cerebrum, (2) Tumor of the Pineal Body in a Boy, Tr Path Soc London **50** 4, 1899

13 De Monchy, S J R Rhythmic Convergence Spasm of the Eyes in a Case of Tumor of the Pineal Gland, Brain **46** 179, 1923

14 Takeya Die Erkrankungen der Epiphysis, Nisshin-Igaku (Japan), 1913, vol 3, part 2, cited by Fukuo, Y Ueber die Teratome der Glandula pinealis, Inaug-Dissertation, Munich, 1914

15 Kishenski, D P, and Tisenhausen, M M von Teratoma of the Cerebellum and Neuroma of the Falx Cerebri in One and the Same Patient, Med Obozr **74** 807, 1910

16 Hueter Teratom der Zirbeldruese, Munchen med Wchnschr **60** 895, 1913

toma Furthermore, Oestreich and Slawyk's case¹⁷ of psammoma cysticum of the pineal gland was diagnosed as a teratoma by Askanazy These cases are mentioned here merely for the sake of completeness

Judged from the recorded cases of teratomas and teratoid tumors, the pineal and pituitary glands seem to produce more tumors than the other intracranial structures Krabbe,¹⁸ who made an extensive study of the pineal gland, explained this high incidence of epiphyseal teratomas by the fact that during intra-uterine life the germ of the gland comes near the surface, nearer than any other part of the brain, and for this reason there are to a superlative degree conditions facilitating the penetration of foreign tissue elements into the organ Other less frequently observed locations are the choroid plexus, the tela choroidea of the third ventricle, the brain substance itself, the region of the tuber cinereum, the cerebellum the cerebellopontile angle and the inner surface of the dura mater Teratoids and teratomas of the spinal cord are of even rarer occurrence, there being only about six verified cases on record In the collection of the Albany Medical College there is a teratoid tumor of the lumbar spinal cord, successfully removed by Dr Arthur H Stem, which was associated with a spina bifida occulta and a pilonidal cyst The microscopic picture showed an overgrowth of smooth muscle cells in which were embedded glandular structures lined by ciliated and non-ciliated cuboidal to columnar cells, some in papillary formation, a few fat cells, nerve fibers and numerous pacinian tactile corpuscles Intracranial teratomas have also been found in the rabbit by Margulies¹⁹ and Shima²⁰ Comprehensive teratologic studies have been made by Wilms,²¹ Bostroem,²² Ewing and Hej1²³ In the case here reported, the cerebellar teratoma was associated with congenital deformities else-

17 Oestreich, R and Slawyk Riesenwuchs und Zirbeldruesen-Geschwulst, Virchows Arch f path Anat **157** 475, 1899

18 Krabbe, K H The Pineal Gland Especially in Relation to the Problem of Its Supposed Significance in Sexual Development, Endocrinology **7** 379, 1923

19 Margulies, A Ueber ein Teratom der Hypophyse bei einem Kaninchen, Neurol Centralbl **20** 1026, 1901

20 Shima, R Ein Teratom im Kaninchenhirn, Arb a d neurol Inst a d Wien Univ **14** 373 1908, Marburg demonstriert fuer Shima aus Tokio, Neurol Centralbl **27** 889, 1908

21 Wilms, M Ueber die Dermoidcysten und Teratome mit besonderer Beruecksichtigung der Dermoide der Ovarien, Deutsches Arch f klin Med **55** 289, 1895

22 Bostroem, E Ueber die pialen Epidermoide, Dermoide und Lipome und duralen Dermoide, Centralbl f allg Path u path Anat **8** 1, 1897

23 Hej1, C F Die Morphologie der Teratome (Mit besonderer Beruecksichtigung der Zentralnervensubstanz), Virchows Arch f path Anat **229** 561, 1920-1921 Beitrag zur Kenntnis von den Teratomen, Ergebn d allg Path **20** 213 1923-1924

where in the body—dwarfism, kyphosis and scoliosis. This association of two or more congenital anomalies is of course, not an uncommon observation.

In a survey of the literature on the various congenital defects, excluding those of the generative organs, one is struck by the fact that males are generally more frequently affected than females. No acceptable explanation has been offered for this. As shown in table 1 of the teratoma group there were 15 males to 2 females, with the sex not mentioned in one case. Seventy-eight per cent of the patients were below the age of 20 years. As regards the teratoid tumors (table 2), there were 14 males to 8 females. Over 52 per cent of these were below 20 years in age. The 19 pineal gland tumors, with one exception, have all occurred in the male sex between the ages of 5 1/2 and 27 years. For the pituitary tumors, there were 3 males to 6 females. In regard to sizes, these growths varied from that of a split pea to 8 by 10 by 12 cm. They were generally cystic.

Histologically, ectodermal and mesodermal elements occurred most frequently. The only structures that might be regarded as entodermal were the embryonal tissue resembling the choïda, the cystically dilated spaces lined by tall goblet cells, and the respiratory epithelium in close relation to cartilage. Other entodermal organoid structures have not yet been described as occurring in these intracranial tumors. Among the teratoid tumors, 21 showed both ectodermal and mesodermal structures, while in 2 cases, only the mesoderm was represented. Malignant changes of a sarcomatous nature were described in 4 cases and in 2 an epithelioma.

From tables 1 and 2, it is seen that all of these tumors arose at or somewhere near the midline. It is well known that the midline in the development of the individual has great potentialities for the misplacement of embryonal tissue and its subsequent maldevelopment. Whether the misplaced cells be totipotent or not will naturally depend on how early such misplacements take place. For the cells to be totipotent, this must occur before gastrulation, when the differentiation into ectoderm and entoderm begins.

SUMMARY

Genuine teratomas of the brain are rare. Another case is here reported, showing derivatives of the three primitive germ layers. Clinically, the patient showed dwarfism, kyphosis, scoliosis, hirsutism, marked hydrocephalus and moronic feeble-mindedness. He was never able to walk. The tumor probably originated from some misplaced tissue in the cerebellum. The literature on teratomas and teratoid tumors is reviewed.

General Review

THE LAW OF THE DEAD HUMAN BODY*

OSCAR T SCHULTZ, M D

Director of Laboratories, St Francis Hospital

EVANSTON, ILL

For the pathologist, using this term broadly to include the hospital or university pathologist, the coroner's physician, the autopsy surgeon, as the California coroner's law styles the coroner's physician, the medical examiner, the medicolegal expert and the physician who is called on occasionally to make a postmortem examination, the dead human body is the chief field of labor. That the body is dead when it is brought to the attention of the pathologist is usually evident enough. The body is dead when all evidences of vitality have ceased. For the determination of death the textbooks give a number of classic tests. The application of these when there is any doubt about the matter of death, usually devolves on the physician who has been in attendance on the deceased at the time of death. The rare instances of suspended animation may occasionally make it necessary for the pathologist to assure himself that the body before him is actually dead. From what appears in the legal literature, and especially in that relating to still-birth in connection with which the question of death has received most discussion in the law, cessation of respiration is the most important factor in determining the moment or actuality of death. The attitude of the legal mind toward the "breath of life" is somewhat akin to that of the poet or of the philosopher, whose discourse is of the soul.

Although it cannot speak for itself, the dead human body has certain rights and privileges, guaranteed to it by the common law and by statute. It is hedged about with legal restrictions just as is the living body. Some of the rights and restrictions relating to the dead body appertain to it because of the wish of the deceased expressed during life. Others are the results of rights which the kin of the deceased have in his dead body. The purpose of still others is the safeguarding of the public welfare, in order that public decency may not be outraged or the public health endangered. The rights of the dead human body and the rights of others in it, as well as the restrictions relating to it, must be observed by the pathologist as well as by all others.

In its study of matters of medicolegal interest, the Committee on Medicolegal Problems of the Medical Section of the National Research

* Submitted for publication Feb 11, 1930

Council made a survey of the offices of coroner and medical examiner as those offices function in the United States. The results of this study were presented in a report¹ published in 1928. A second task undertaken by the Committee was to have prepared a digest of laws and court decisions relating to the dead human body. This compilation was made by Mr. George H. Weinmann.² It is on the matter presented by Mr. Weinmann that this review is based, its aim being to present to the pathologist such aspects of the subject as are of interest and importance to him in his work. References to legal writings will, in general, be omitted, when given, they will be in the form adopted in legal writings. The subdivision of the subject matter used by Mr. Weinmann will be adhered to, to facilitate reference to the original bulletin and to the numerous legal citations therein given.

WHAT IS A DEAD HUMAN BODY AND WHEN DOES
IT CEASE TO BE SUCH?

Law, which deals in exact definitions and in finely drawn distinctions which often require court decisions for their interpretation and further precision, does not set down in so many words just what a dead human body is. The term "dead body" is frequently used in the statutes, especially those relating to the coroner, and in general is synonymous with "corpse," derived from the Latin *corpus*, which in its turn means again simply body, but in older religious and philosophic writings, the body as opposed to the soul and such other supermechanistic attributes as the living human being was supposed to possess. The terms "dead body" and "corpse" suggest a human being who has been deprived of life. The signs of death and the tests for determining the cessation of life are described in the textbooks of forensic medicine. Law lays greater stress on the cessation of respiration as an evidence of death than on the extinction of any of the other vital functions.

But the human body from which life has passed does not always remain a dead human body in the legal sense. Court decisions have held that it ceases to be such when it is completely decomposed or disintegrated, and that the laws relating to the disposal of the dead human body no longer apply to the more or less completely disintegrated remains of the human body. After presenting two court decisions pertaining to this subject, Weinmann³ said

1 Schultz, O. T., and Morgan, E. M. The Coroner and the Medical Examiner, National Research Council, Bull. 64, 1928.

2 Weinmann, G. H. A Survey of the Law Concerning Dead Human Bodies, National Research Council, Bull. 73, 1929.

3 Weinmann (footnote 2, p. 10).

Thus, we see that the courts have definitely committed themselves to the rule that mere remains of a body of a person long dead are not to be considered as a dead human body. In the first case the remains were those of an unknown person who had apparently never been buried. In the second case they were those of a person who had once been interred. It is true that in both these cases interpretation of statutes was involved, but these statutes in no way necessitated an unusual interpretation being placed on the terms "dead body" and "corpse."

This is, perhaps, the answer to the facetious question "When does the removal of human remains from their burial place cease to be grave robbery and become archeology?"

PARTS OF THE BODY

The interpretation of laws relating to parts that have been removed from the living body is a matter of especial interest to the hospital pathologist. In my work as pathologist to hospitals I have performed my labors under the impression or assumption that parts or organs removed from the body during surgical operations belong to the hospital, on which devolves the duty of making disposal of such parts and which therefore has the right to make such disposal as it may deem best. I had believed that the surgeon, through courtesy, stood next in the line of possession. Such is not the case. Removed portions of the body belong to the person from whom they have been removed. He has the right to specify what disposal is to be made of them and may bring action to recover damages if the disposal has been contrary to his wishes. The mendacious patient might make this knowledge a source of trouble. It might be well for hospitals and surgeons to protect themselves against the possibility of lawsuit by including in the operating permit, which the patient or his legal representative signs, a statement covering the disposal of parts removed at operation.

The right of the individual to the possession or disposal of parts removed from his body is a right accruing to him under the common law. Positive statutory enactments defining this right of the individual are in force in New York, North Dakota, South Dakota and Oklahoma. The North Dakota statute⁴ relating to this matter, which has been adopted also by South Dakota and Oklahoma and which is almost as restrictive as are the laws governing the disposal of the dead human body, is as follows:

All provisions of this chapter requiring the burial of a dead body or punishing interference with or injuries to a dead body apply to any dead limb or member of a human body, separated therefrom during lifetime.

Since the provisions referred to relating to the dead body require burial permits and permits for removal or exhumation, a strict inter-

⁴ Section 9623, Compiled Laws of North Dakota 1913

pretation of the law quoted would make similar regulations apply to parts removed from the living body

STILLBIRTHS

Although there is considerable variation in the different states in the definition of stillbirth, the statutory provisions or the regulations of the department of health or vital statistics requiring the registration of such births, in effect in most of the states make of the body of the stillborn infant a dead human body in the legal sense. The laws relating to the disposal of the dead human body therefore apply to the stillborn infant. Such discrepancy as exists in the laws of the various states centers about the period of uterine gestation that the fetus must have reached before it can be considered a stillbirth rather than a miscarriage. This period varies from the fourth to the seventh month of pregnancy in the different states. In order to bring about uniformity, Weinmann recommended the adoption by all the states of the definition of stillbirth proposed by the International Health Board of the League of Nations. The proposed definition of "birth" "live-birth" and "dead-birth" follows

It is requisite, in drafting the desired definition, to have a clear understanding of what constitutes a "birth" and when such "birth" is "complete"

In the proposed definition the word "birth" means the separation and extrusion of a foetus from the body of the parturient woman. The birth is to be deemed complete at the instant when the whole of the body of the foetus—head, trunk, and limbs—is outside the body of the mother.

The birth is to be deemed a live-birth if, after birth (as defined above) the infant breathes.

The act of respiration is incontrovertible evidence of life, and its continued absence is to be taken as proof of foetal death.

It is desirable, for statistical purposes, that a distinction should be made between the birth of a foetus which can normally be expected to be capable of an existence independent of its mother and the expulsion of one which cannot, births in the latter category being regarded as miscarriages (abortions).

A foetus capable of an independent existence is a "viable foetus" and is the product of a gestation which has lasted at least twenty-eight weeks. Such foetus will normally measure at least 35 cm from the crown of the head to the sole of the heel, the body being fully extended. We are of the opinion that the latter criterion is the more trustworthy.

Hence, a "dead-birth" is the birth of a foetus, after twenty-eight weeks' pregnancy in which pulmonary respiration does not occur. Such a foetus may die either (a) before, (b) during, (c) after birth, but before it has breathed.

Under existing conditions, two criteria obtain in determining in any given case whether the child was stillborn or died immediately after birth. The child must have been completely delivered, that is the cord must have been severed and independent respiration must have been established if the child is to be considered a living infant. In the

legal sense, an infant who begins to breathe after its expulsion from the vagina, but ceases to breathe before the cord is severed, is stillborn.

Registration of stillbirth makes the stillborn infant a dead human body. The laws regulating the disposal of the latter therefore apply to stillbirths. In many localities, however, they are loosely construed. Disposal to a hospital or to a physician, instead of in a recognized burial place or licensed crematory, is usually permitted. The final disposition made by the hospital or physician may be such as would not be permitted in the case of other dead bodies. Many pathologists probably have the same feeling of lack of legal responsibility in regard to stillbirths as to removed parts of the body. They should protect themselves against mendacity and possible lawsuits by assuring themselves that disposal has been granted in proper legal form before anything is done which might be construed as mutilation of the body.

PROPERTY RIGHTS

The Right of Custody—The dead human body is not property in the legal sense. It may not be bargained for, bartered or sold. Most states have drastic laws against the sale or illegal possession of the dead human body. It may be disposed of only in such manner as is recognized by law, that is, by interment or cremation, if there is any one on whom the duty of disposal devolves. The right of custody and the duty of legal disposal are concomitant. The right of custody usually follows the laws of inheritance of property, nearness of kinship of surviving relatives determining the custody. The right of custody does not, however, follow the rules of inheritance in all cases. If the deceased had been married but had been separated before death from the surviving spouse, the right of custody rests with the nearest of kin and not with the surviving spouse. Some odd and little known common law provisions relate to the duty of burial, if the deceased had no known relatives or friends on whom the duty of burial devolves. If there are no statutory provisions specifically regulating the disposal of such dead bodies, the common law places the responsibility for burial on the tenant of the building in which the death occurred or on the owner if there was no tenant. Under similar circumstances, the master of a vessel on which death occurred must make proper legal disposal of the body, if there is no master, the owner is responsible. The duty of burial of a person without kin or kin falls on the administrator or superintendent of a hospital in which the death occurs. In most states these common law rules have been superseded by the laws creating state anatomic boards, by laws empowering the coroner to bury if an inquest has been held or by laws providing for the burial of the indigent.

The right of custody and the duty of burial have bearings which are important to the pathologist. They influence the right to give consent for the making of postmortem examination. This matter is discussed in greater detail in a later section.

Testamentary Disposal of the Body—Although the English law, on which our common law is based, does not recognize the right of a person to dispose of his body by will, most of our states do recognize such a right. New York, North Dakota, South Dakota and Oklahoma have enacted laws specifically granting the right of a person to dispose of his body or parts thereof by will. In other states such right has generally been upheld by the courts. Although the person legally entitled to the custody of the dead body, in the absence of testamentary provision for its disposal, has no property right in the body the living person does appear to have such a right in his own body. He may specify by will the place of burial of his body or the manner of disposal, whether by burial or cremation. He may require that a necropsy be done. He may dispose of parts of his body for scientific purposes. He may even barter or sell his dead body, receiving payment therefor during life, provided the disposal to be made of his body does not outrage public decency or menace the public health. An interesting court decision⁵ upholds the validity of an insurance policy clause by which the insured grants to the company the right to have a necropsy made if the company deems such an examination advisable.

From the legal point of view questions arising out of violations of the right of custody of the dead body or of quasi property rights in such body are vexatious. They involve the always troublesome problem of money damages for mental pain and suffering when there has been no physical damage. A few jurisdictions recognize no such form of damage. In jurisdictions that do recognize such damage, the amount of money damage allowed may be merely nominal or it may be punitive. The class of case in which this question of violation of rights in the dead body most frequently arises is that in which damages are asked for the making of an unauthorized necropsy. In his discussion of the subject, under the heading, "Remedies," Weinmann⁶ said

Summing up this whole question of damages, we might say that it seems to be well settled that damages for mental pain and suffering are recoverable for the invasion or violation of, or interference with, the various rights connected with the custody and interment of the dead, despite the fact that it is a well-recognized general rule of damages that mental suffering, in order to be an element of damage, must be connected with some physical injury, and that it must be the proximate result of such physical injury.

However, some violations of rights are not such as could be compensated for. If, for example, the legal custodian of a body were deprived of its possession

5 Weinmann (footnote 2, p. 28)

6 Weinmann (footnote 2, p. 33)

prior to the burial, we have seen that he could bring an action at law for money damages. But ordinarily, that would not satisfy the person aggrieved. Therefore, if he wishes to have the actual possession of the body and not to be compensated for the violation of his rights, he should properly go into a court of equity. There is no general rule to be applied to determine how and when the courts will act in such cases beyond the general principles we discussed when treating the subject of custody. Each case will be decided by an equity court on its own merits, and the general equity principles of substantive and procedural law will be applied. In a court of equity, and only there, can one have his rights specifically enforced.

The Coroner and the Dead Body—The coroner may be conceded to have absolute control of any dead body which he must view or over which he must hold an inquest. His control is generally conceived to be so broad as to lead to the belief that the body of a human being, whose death he must investigate may not be disturbed or moved until viewed by him or until he has given permission for its removal. So far as disturbance of the body may interfere with the investigation or detection of crime, the matter is important. But neither in common law nor in the statutes of the states and territories of the United States is there any specific statement prohibiting removal of the body. Removal of a dead body over which the coroner has authority might be punishable on the ground that such disturbance is an interference with the proper discharge of the duties of an official or is an attempt to destroy necessary evidence, but the intent to interfere or to destroy evidence would have to be proved. After full discussion of the subject of removal of the dead body over which the coroner has jurisdiction and after presentation of the statute of each state and territory relating to this subject, Weinmann⁷ concluded:

After having gone through this brief resume of the laws of the various jurisdictions, we note that in very few instances do we find any intimation or express statutory provision, prohibiting the person who may discover a dead human body from moving it prior to a view by the coroner. However, as pointed out at the beginning of this chapter, it has always been a violation of the law to hinder the coroner in the performance of his duties. Therefore, one should never move a body, even where it is permissible, prior to having been granted permission from the proper authorities, unless it becomes absolutely necessary. Mere meddling would not be tolerated in the most liberal-minded jurisdiction. In cases where there is reason to suspect crime, evidence of a very important nature may be destroyed by the slightest disturbance of the body. It is even possible, too, for the person who has a tendency to meddle in this respect to incriminate himself unwittingly.

Therefore, although as a general rule it would appear that there is no prohibition against moving a body, it is compatible with common prudence and wisdom to allow the body to remain in the same position in which it was discovered until the proper authorities have viewed it.

⁷ Weinmann (footnote 2, p. 57)

Although the section, which is entitled "Coroners and Coroners' Inquests" and of which the quotation given is the conclusion, deals with what may appear to be a question of minor importance, in that it relates chiefly to the removal of the dead body, it contains matter of great value to everyone interested in criminal justice. It gives, for the first time so far as I am aware, a compilation of the statutes of the various jurisdictions of the United States relating to the duties of the coroner.

NECROPSIES

Consent—The laws which hedge about the dead human body and which protect the rights of those entitled to its custody require consent for the postmortem examination of such a body. The unauthorized performance of a necropsy is a ground for a civil suit for damages and in some states is a violation of the criminal code. The pathologist, who takes pride in his work, who feels that he performs that work with due respect to the dead and to the feelings of the living, and who looks on his work as useful, will probably be amused, perhaps a little painfully, by the following words of a learned judge in rendering a decision in a suit⁸ in which the unauthorized performance of a necropsy was alleged.

The right is to the possession of the corpse in the same condition it was in when death supervened. It is the right to what remains when the breath leaves the body, and not merely to such a hacked, hewed and mutilated corpse as some stranger, and offender against the criminal law, may choose to turn over to an afflicted relative.

It is possible that his amusement may be tinged with indignation at the implied description of his work as a process of hacking, hewing and mutilating the dead body.

In general, the consent for a necropsy may be given by the person who is entitled by law to the custody of the body and who is charged with its burial. This subject has already been discussed, and it was noted that under certain circumstances the tenant or owner of the building, the master or owner of the vessel, or the superintendent of the hospital, in which death took place, is charged with burial. Such a person, therefore, has the right to give permission for postmortem examination. In most states, however, this right is curtailed by the provisions of the anatomical acts which have been made part of the laws of such states.

Consent need not be in writing or in any specified form, unless specifically so provided by legislative or departmental enactment. The consent, even the necessity, to perform a necropsy may be a provision

⁸ *Foley v. Phelps*, 1 App. Div. (N. Y.) 551.

of the will of the deceased. It has already been noted that a clause in an insurance contract granting to the company the right to demand a postmortem examination has been held valid by the courts. Even without definite statutory provision to that effect, the coroner or medical examiner has the right to authorize a necropsy in any case in which it is necessary for him to determine the cause of death, unless such right has been specifically limited or curtailed by legislative enactment.

Legislative Enactments Relating to Necropsies—Although the right of the person entitled to custody or of the coroner to authorize a necropsy may in general be taken for granted, laws have been enacted in certain states which seem to limit the right of authorization for such examination, or which make specific requirements regarding such authorization, or which make postmortem examination mandatory in certain cases. A number of states require necropsy of executed criminals, in Hawaii, there is the interesting regulation that the high sheriff shall deliver the body of an executed criminal "to any surgeon who may wish to have such a body for dissection." The law of Connecticut specifies that the consent for necropsy of patients who die in hospitals must be in writing, and that hospital authorities may authorize an autopsy if, after due diligence, they cannot locate any relatives or friends entitled to the custody of the body, but provides further that the autopsy shall not be done until a reasonable time, not exceeding forty-eight hours, has elapsed. The Illinois statute contains an anomalous provision that has led some coroners to contend that a necropsy may not be held in that state unless authorized by the coroner, even if those legally entitled to give permission for the performance of an autopsy wish such an examination made. This contention is based on the final sentence of chapter 31, section 10, of the Revised Statutes of Illinois, which reads as follows:

In any case where a person is supposed to have come to his or her death by violence of a criminal character as aforesaid, and in cases where the cause of death is not known, and concerning which the circumstances evidence violence of a criminal character, or death from criminal means, or where said cause of death is unascertainable otherwise than by autopsy, the coroner may, in his discretion, either before or after the jury is summoned and sworn, call a physician to examine the body of the deceased, and if from examination, or from a preliminary investigation by the coroner, the cause of death cannot be definitely ascertained by the coroner, he may in his discretion, or the jury after being summoned and sworn, may, in its discretion, order and direct an autopsy to be held upon the body to ascertain the cause of death. In all cases where the coroner has reasonable ground to believe or suspect, or where there is any evidence, that death resulted through criminal means or agencies, it shall be his duty to conduct a postmortem examination upon the body. *Provided*, however, that there shall be no autopsy ordered, directed or held except as heretofore in this section expressly provided.

It will be noted that the foregoing statute defines the conditions under which the coroner may perform or order an autopsy, and that it gives him wide authority in this respect. The two clauses that read "in cases where the cause of death is not known" and "or where said cause of death is unascertainable otherwise than by autopsy" would seem to give the coroner unlimited latitude in the matter of postmortem examinations. The final provision of the section, which states very clearly that a necropsy shall not be held except as provided in the rest of the section, which relates entirely and only to the authority of the coroner in such matters, would appear to prohibit the performance of an autopsy, even if consent has been given by surviving relatives, unless the coroner also authorizes the examination. If a suit brought against a coroner, ostensibly to limit his powers, should result in a decision upholding the constitutionality of the section as a whole, there will arise the possibility of interference with postmortem examination by an unfriendly coroner or undertaker, as well as the further possibility of a suit for damages if an autopsy is held with the consent of the relatives but without the express consent of the coroner. The Illinois statute leads one to feel that the laws of each state relating to the powers of the coroner should receive closer scrutiny by those interested in the development of medical science through postmortem examination than such laws have received.

In Louisiana, in addition to the statutory provision authorizing the coroner to hold a necropsy whenever deemed necessary by him, there is a regulation of the state department of health that permits the board or any local health officer to order a postmortem examination of any person or animal dead of a suspected communicable disease.

In Massachusetts and some of the other New England states that have adopted the medical examiner system, the authority for ordering a medicolegal necropsy is vested in the legal arm of the government. Nominally, at least, the medical examiner functions when ordered so to do by the attorney general, the district attorney, the mayor or the selectmen. In Oregon the coroner acts on direction of the district attorney. In Maine, which has the medical examiner system, the statute requires that a necropsy held by the medical examiner be made in the presence of a physician and one other "discreet person."

The Michigan law relating to necropsies appears at first glance to be restrictive. It is, however, definitive rather than actually restrictive. After stating that "the right to dissect the dead body of a human being shall be limited to cases specifically provided by statute," the law goes on to say that an autopsy may be done when authorized by the coroner, or by direction or will of the deceased or when consent is given by the next of kin or by the person charged with the burial of the body. The extent of the postmortem examination may be limited by the person

authorizing its performance. Another Michigan statute gives the Industrial Commission the authority to order an autopsy if such examination is considered necessary in the settlement of death claims. Still another section provides that every autopsy performed by a coroner shall be held at a public morgue, if there is no public morgue, then the necropsy must be done at the residence of the deceased.

North Dakota, Oklahoma and Oregon recognize the authority of the coroner to hold or order an autopsy, the right of the person entitled to custody of the body to give permission for necropsy and the power of the legislature to enact specific provisions relating to necropsies. South Dakota, in addition to similar general provisions, specifically authorizes the postmortem examination of those who die while under medical care in a charitable institution maintained by the state, provided the next of kin have apparently neglected or abandoned the inmate. Failure to have made inquiries concerning the inmate during a period of six months preceding his death is defined as neglect.

The ordinances of the City of Manila, in the Philippine Islands, give to sanitary inspectors the right to demand a necropsy if there is reason to believe that the cause of death is different from that stated in the certificate of death. The Administrative Code provides for the aid of the department of legal medicine of the College of Medicine of the University of the Philippines in any death the cause of which is not satisfactorily explained. This would appear to be a nearer approach to making available the services of a university department of legal medicine in work of the kind usually done by the coroner than that which prevails in any part of the continental United States.

ANATOMICAL ACTS

Laws regulating the disposal of unclaimed dead bodies have been enacted by all states except Arizona, Delaware, Florida, Idaho, Louisiana, Maryland, Montana, New Mexico, Nevada and Rhode Island. The purposes and restrictions of the anatomical acts as they have been termed, are much the same in the various states that have such acts.

Dead human bodies to which the anatomical acts apply are those which would have to be buried at public expense. They are bodies that are not claimed by relatives or friends, who would have to bear the expense of burial. The agencies that have control of such bodies at the time of death are usually those charged with the care of the indigent or criminal. These agencies are specified in the Arkansas law as follows: "the board of health of any city, village or township, the mayor or common council of any city, and the officer or board having direction or control of any almshouse, prison, house of correction or jail." In California the agencies which may have control of the body

at the time of death are the "sheriff, coroner, keeper of a city poor-house or reformatory, public hospital or asylum, county jail, State prison, or city or county undertaker, or any and all State, county, town and city officers having possession, charge or control of bodies to be buried at public expense" This state has the further interesting provision that if a body becomes "unfit" for educational purposes through neglect of the responsible person promptly to notify the board that he has such a body in his possession, the body is to be buried at the expense of the negligent official

Practically every state that has an anatomic law exempts the bodies of travelers and strangers from the provisions of the law In the Philippines the law does not apply to the bodies of prisoners In most states, the disposal provided for by the anatomical act is not effective if the deceased has requested during his last illness that his body be buried The Tennessee law does not apply to counties with a population of 4,000 or under The unclaimed bodies of those dead of contagious disease do not come under the provisions of the anatomical acts of most of the states

Some of the acts specify a period of forty-eight hours following death during which the body may be claimed by relatives or friends for burial Other states require that immediate notification be given by telegraph to the authority that has control of unclaimed bodies In Alabama, notice of the death of a supposedly friendless and destitute person must be posted on the door of the courthouse for forty-eight hours following death Most states specify a period of time, which varies from twelve to sixty days, during which the body must be held by the final recipient before it may be used for the purposes stated in the act If, during this period, the body is claimed by any one who is willing to defray the cost of burial, it must be surrendered without question

Bodies, the disposal of which is covered by the anatomical acts, are in many instances those of persons on whom the superintendent or other administrative official of a hospital could, under the common law, grant permission for necropsy As the acts abrogate this right, the pathologists may be inclined to feel a certain degree of hostility toward them The legal custodian of the body under the act may, however, grant permission for postmortem examination if the latter is deemed necessary or advisable

Without such authorization, pathology has precedence over anatomy in a few instances The act of Georgia specifically states that autopsies may be done on the bodies of patients who die in the Georgia State Sanitarium The Augusta State Hospital and the Bangor State Hospital of Maine need not surrender bodies to the anatomical board, but may themselves conduct autopsies, postmortem examinations and dis-

sections "for the advancement of medical science" Massachusetts also gives precedence to the autopsy, if the cause of death cannot be otherwise ascertained. New York recognizes the right of the person in charge of a hospital to order a necropsy, unless objection is made by the next of kin, in the case of unclaimed bodies, however, the medical schools have a prior claim on such bodies for the purpose of teaching anatomy.

The purpose of the anatomical acts is usually stated to be the advancement of "medical science," "anatomic science," "medical knowledge" or "medical teaching." They furnish material for the dissecting room. In so doing, they have wiped out the scandals of grave robbery and of the illegal sale and transportation of dead human bodies. The latter purpose is recognized in the act of the District of Columbia which is entitled "An Act for the Promotion of Anatomical Science and to Prevent the Desecration of Graves in the District of Columbia." All of the anatomical acts provide that the body must be used within the state in which death occurred. Sale or transportation outside the state is punishable by fine or imprisonment or both. On the other hand, interference with the provisions of the act is also punishable.

The agency provided by the anatomical act for carrying out the provisions of the latter varies in different states but is much the same in general principles. This agency becomes the legal custodian of the unclaimed dead body and makes distribution of such bodies in accordance with regulations named in the act itself or drawn up by the agency. The latter may be the state board of health, an anatomical board provided for by the act or named by the deans of the medical schools of the state, or the state or some other university.

The final distribution of bodies the disposal of which is provided for by the anatomical acts is, in general, to medical schools. The distribution is made according to the number of students enrolled. The Connecticut law specifically names the school of medicine of Yale University the recipient of unclaimed bodies. In Michigan, the act provides that the bodies of those who die outside the limits of Wayne County shall go to the University of Michigan, the Detroit College of Medicine and the Detroit Homeopathic College are made the recipients of the bodies of those who die within Wayne County. The University of Wisconsin receives the bodies from the western United States judicial district of the state, Marquette University those from the eastern federal judicial district. Mississippi, South Dakota, Utah and West Virginia name the state university in their acts.

Iowa gives recognition to osteopathy and chiropractic schools in the following

The body shall be delivered to the medical college of the State university or some osteopathic or chiropractic college or school located in this State,

which has been approved under the law regulating the practice of osteopathy or chiropractic

In some states, schools of dentistry may receive bodies. Kansas, North Carolina and Virginia grant to schools for the teaching of embalming the same privileges as to medical schools.

Alabama, Illinois, New Hampshire, North Dakota, Pennsylvania, South Carolina, Vermont and Washington permit distribution of dead bodies to individual physicians and surgeons and to associations other than medical colleges. In most of these states the medical schools have the prior claim, individual physicians receiving bodies only if there is a surplus above the needs of the schools. In New Jersey, the official who has charge of an unclaimed dead body is required to give notice to the pathologic and anatomical associations of the county, and to surrender the body to either or both of these associations on request.

Some states, especially those that require that the body be held for a considerable time before it is used for dissection, require that the body be embalmed. Other states make no mention of embalming. All demand that the portions left after dissection be interred, cremated or disposed of in such manner as will not outrage public decency. In some states an approved bond must be filed before a body may be received by a school or a person.

EVIDENCE AND THE QUESTION OF PRIVILEGE IN RELATION TO THE DEAD BODY

Information gained by a physician from another person, when the relationship between the two is that of physician and patient, is privileged and as a general rule is not admissible as evidence. Although the common law does not recognize the privileged character of communications between physician and patient, many states have enacted statutes that prohibit a physician from divulging information gained by the treatment of a patient or through communications made by the latter. The federal courts also recognize the rule of privileged communications.

As a general rule, information gained by the performance of a necropsy is not privileged and is therefore admissible as evidence. A state of confidentiality, which is the basic principle that makes communications privileged, cannot exist between a dead body and a living person. A court decision⁹ expresses the matter thus:

A dead man is not a "patient," capable of sustaining the relation of confidence toward his physician which is the foundation of the rule given in the statute, but is a mere piece of senseless clay which has passed beyond the reach of human prescription, medical or otherwise.

⁹ *Harrison v. Sutter State Railway Company*, 116 (Calif.) 156.

The claim of privilege has a number of times been set up in court actions with the object of preventing the admission as evidence of information gained by postmortem examination. Courts have consistently refused to allow the claim, and have admitted as testimony facts learned at necropsy.

In at least one instance,¹⁰ information gained through postmortem examination has been held inadmissible as evidence on the ground that it was privileged. In this case, the autopsy was done by the physician who had attended the deceased during her last illness. The court held that the physician's attendance on and treatment of the deceased during her lifetime had materially aided him in the performance of the autopsy and in the determination of the cause of death.

LIABILITY FOR UNAUTHORIZED NECROPSY

It has been noted in a previous section that necropsies may be done only when consent thereto has been given by those entitled to the custody of the body or charged with the duty of its burial, or when ordered by the coroner, or when made necessary by specific statutory enactment. An autopsy done under any other conditions is unauthorized and renders him who performs it liable to suit for damages.

In determining the liability for and the amount of damages, several important questions enter into consideration. Since there exists no right of property in the dead human body, it has been maintained by some that no property damage is done in the performance of an unauthorized autopsy. There does exist, however, a right of custody to the dead body, as well as a right or duty of sepulture. An essential element of these rights is possession of the body in the same condition it was in when the breath of life left it. Interference with or violation of these rights is a wrong or injury, for which the injured person may go to court. It is in their decisions on this subject that learned judges make frequent use of "mutilation," "desecration" and other opprobrious terms. Courts have been unanimous in the opinion that a person wronged by an unauthorized postmortem examination of a body, to the custody of which he is entitled, shall be compensated.

A question that appears to be in an unsettled state relates to the liability of the physician who does an unauthorized necropsy because he considers such an examination necessary to ascertain the cause of death, in order to be able to comply with the regulations concerning death certificates and burial permits. In one of the citations given by Weinmann,¹¹ the claim for damages was upheld. In other cited cases, courts have ruled that such an autopsy does not render the physician liable to damages if it has been done in a proper manner. Having a

10 *Thomas v Township of Byron*, 168 (Mich.) 593

11 Weinmann (footnote 2, p. 88)

bearing on this matter of unauthorized autopsies is the ruling that the making of a slight incision for the purpose of determining the cause of death, there being no dismemberment or removal of organs, is not mutilation of the dead body in a sense that gives cause for legal action.

When an unauthorized autopsy is done for the avowed purpose of determining the cause of death, in order that the death certificate may be properly made out, the decision of the courts of any given state would probably be influenced by the statutory and departmental regulations governing death certificates and burial permits. If a physician honestly feels himself unable to state the cause of death probably the safest course for him to pursue is to place on the coroner or medical examiner the responsibility of authorizing the certificate of death or a necropsy if the latter is necessary.

The removal of parts or organs from the body, consent for necropsy having been given in proper form, has also engaged the attention of the courts. Most pathologists and hospital administrators probably believe that when no verbal or written restrictions are included in the consent for necropsy, the latter may be as complete and as thorough as the pathologist deems necessary. In the first place, it is to be noted that the person entitled to give permission for necropsy is entirely within his rights in placing on the necropsy whatever restrictions he chooses. Any violation of the restrictions would be cause for legal action. Furthermore, it has been held that, an autopsy having been authorized, the doing of anything more than is actually necessary to determine the cause of death is not permissible. Weinmann¹² said that a "physician cannot legally remove and retain portions of the body, unless such procedure is essential for determining the cause of death or for the determination of some other reason for which the autopsy was ordered or permitted." In a case¹³ in which a father alleged that organs had been removed from the body of his son during an autopsy and had been illegally retained or disposed of, the court made the following strong statement:

While it may be true there is no right of property in a dead body, in the ordinary sense, it is also true that the nearest relatives of the deceased are and always have been in all ages, so far as known, except under ecclesiastical law, recognized as legally entitled to its custody, to lay it away in burial. It is the duty no less than the right of such relatives to protect it from unnecessary violation, and any infringement upon that right, except where made necessary for the discovery and punishment of crime, violates the tenderest sentiments of humanity.

Unless sufficient reason existed for an autopsy he was entitled to the body unmutated. If such reason did exist, he was, nevertheless, entitled to the whole body, even though necessarily disfigured, unless it proved necessary to remove and preserve some particular organ for further

¹² Weinmann (footnote 2, p. 90)

¹³ Palenzke v. Bruning et al., 98 (Ill.) A. 644

examination, as to whether a crime had been committed, or for evidence. But none—coroner, nor doctor, nor undertaker—had the right to remove parts of the body and, without the parents' consent, throw them into a privy vault. Such conduct violates every instinct of propriety, and could not fail to outrage the feelings of kindred of the deceased. For such violation of appellant's rights an action for damages can, we think, be maintained.

The attitude of the legal mind toward postmortem examination and the fine distinctions it draws between the act, the intent and the letter of the law are not always entirely or easily comprehensible. Judges speak of the determination of the "exact cause of death" as if this were an exact science, or as if it could be done by means of a small incision or by superficial inspection of the organs through a larger incision. Every pathologist knows that the cause of death must often be determined by exclusion, by the careful examination of every important organ of the body in order that he may decide that any given lesion is the cause of death. He knows that he must frequently call to his aid every resource of pathologic histology, chemistry and bacteriology to determine the cause of death. His defense, if accused of carrying a post-mortem examination further than may seem necessary or of retaining anything from the body, would probably be that he alone is competent to decide what is necessary to do in order to determine the cause of death in anything approaching the exact manner that the law seems to recognize.

A final point for consideration is the responsibility of the pathologist who permits any one to witness a postmortem examination. The embalming laws of a number of states, which are discussed in a later section, specifically prohibit the presence of any one during the preparation of a dead body other than those actually necessary for the work. It has been held that the right of privacy, even when such right is recognized, dies with the individual. Yet in the matter of permitting any one to be present at an autopsy, there enters again the question of the feelings of surviving relatives. Whether a pathologist lays himself open to a claim for damages if he permits witnesses at a necropsy, other than a medicolegal one, in which case the presence of witnesses may be required by law, has not come up for adjudication. In the absence of legal precedent, Weinmann¹⁴ gave the following opinion:

It would appear that if the conduct of a person who introduces total strangers into an autopsy room is of such a character as to arouse a feeling of repulsion toward the perpetrator of the act on the part of the next of kin or other relatives or friends, if such action would tend to subject the relatives or kindred to ridicule or unpleasant notoriety, or if such act would be reasonably certain to shock the sensibilities of any person, it would seem reasonably certain that such an act would render the person guilty of it liable in an action for damages.

14 Weinmann (footnote 2, p 91)

It will be seen that he whose duty and work it is to make postmortem examinations exposes himself to the possibility of legal action, if the examination is unauthorized or if certain other contingencies arise in the course of an autopsy for which consent has been given. If the action is a claim for damages, its basis is not a violation of a right of property in the dead body, but a violation of the rights of custody and sepulture, with resulting mental anguish and injury to the feelings of those who have these rights. Mention has already been made of the doctrine of mental pain and anguish. In its relation to unauthorized autopsies, Weinmann¹⁴ discussed it again as follows:

We have already seen that damages for mental pain and anguish have been awarded in cases involving the question of a violation of the rights of sepulture vested in the legal custodians of the body. This same rule holds good in cases of unauthorized autopsies. It will not be necessary to go into the theory of "mental pain and suffering" as that has been done to an extent sufficient for our purposes in a preceding section.

Suffice it to say, that in those jurisdictions allowing damages for injuries to the feelings, a pathologist who performs an unauthorized autopsy, will render himself liable in damages to the extent of being compelled to pay for the damage he has inflicted on the feelings of the persons injured. In jurisdictions which will not allow damages for mental anguish in a case like the one under discussion, the great probability is that merely nominal damages could be collected, for the only theory on which damages are ordinarily assessed is a violation of a right of property. Now we know that no one has a right of property in a dead human body, and therefore the pathologist who performs an autopsy without the consent requisite to make it a valid act, violates no right of property. Therefore, if the court will not allow damages for mental suffering, it would follow that only nominal damages could be awarded. It would be safe to say, however, that in the great majority of cases a person making an unauthorized autopsy would render himself liable to pay for such injury to the feelings—or exemplary damages, as some courts have put it—who do not wish to say that they have allowed damages for mental anguish in such a case.

EMBALMING

In most of the states, regulations relating to embalming deal with licensure of embalmers. Some states have statutory or departmental provisions that are of interest to the pathologist, the medicolegal expert or the public health official, in that they make embalming mandatory in certain cases, prohibit it in certain others or prescribe the ingredients of the material used for embalming.

Colorado, Connecticut, Illinois, Kansas, Maine, Massachusetts, New Jersey, New Mexico, Oklahoma, South Carolina, Vermont, Virginia, Wisconsin, Wyoming, the District of Columbia, the Philippines and Porto Rico prohibit embalming if there is reason to believe that death was due to other than natural causes, unless permission is obtained from the coroner, medical examiner or other proper official. The

wording of the statutes of many of these states is such as to appear to place the responsibility of determining whether permission for embalming is necessary directly on the undertaker or embalmer. If a certificate of death is required before embalming in any case, the undertaker is relieved of the responsibility of determining whether the circumstances of death were such as to require permission.

The composition of the embalming material, especially as it relates to interdicted substances, is covered by regulation in Connecticut, Idaho, Kansas, Mississippi, Nebraska, New Hampshire, South Dakota and Wyoming. The substances most widely prohibited are mineral poisons, of which arsenic and mercury are named in most instances. Some states add zinc, lead, copper, silver or antimony to the list. Since the law is such a stickler for verbal precision, one wonders what an embalming fluid might contain in Mississippi, where such a fluid may not contain "arsenic or other deadly poisons." Chloral, strychnine or cyanogen compounds are not permitted in some states. In certain states, only fluids containing formaldehyde may be used. A statement on the label giving the percentage of formaldehyde, or one indicating that the fluid contains no mineral poisons, may be required. The amount of fluid to be used may be specified, this is usually 5 per cent of the body weight in ordinary cases, and 10 per cent in contagious diseases.

Delaware specifies a long list of contagious diseases in which embalming must be done before the body may be removed from the room in which death occurred. This state also requires that when death was due to smallpox, the body must be "cremated or buried deep." In New York, "before embalming any dead body, or injecting therein any fluid, such tests as shall be prescribed by the supervisor of embalming must be applied, to determine beyond all doubt the fact that life is extinct." In the District of Columbia a body may not be embalmed within four hours of death, unless a certificate of death has been filed and accepted before the expiration of this period. In Arizona and Nebraska, none other than the embalmer and his absolutely necessary assistants may be present in the room where a body is being embalmed or prepared for burial. In the Philippines, "all embalming must be performed only in a morgue properly built so that it is free from flies and other insects."

TRANSPORTATION OF THE DEAD BODY

Regulation of the transportation of the dead human body is delegated in most states to the department of public health or some other similar agency. In addition to such regulations, the transportation is governed also by rules made by the common carrier and by the federal quarantine and customs regulations. In general, transportation requires a transit permit originating at the place where death occurred. A

permit issued by the state into which the body is to be shipped is also required by certain states. A prerequisite for the transit permit is an accepted certificate of death, the issuance of which covers any matters that may concern the coroner, medical examiner, registrar of vital statistics or public health officials.

Other details vary considerably in the different states. The regulations in force in Arizona have been adopted by the National Funeral Directors' Association. The main features of the Arizona regulations are covered in one form or another by the rules of most other states.

When death has been due to certain specified contagious diseases, namely smallpox, plague, Asiatic cholera, typhoid, scarlet fever or diphtheria, the body must be thoroughly embalmed with an approved fluid and must be placed in an hermetically sealed metal or metal lined box. In deaths due to other causes, embalming may not be required if the body can reach its destination within twenty-four hours after death. If a longer period is required, embalming is necessary.

The size of the body box, the number of handles that it must have and the transit labels to be affixed are often specified. Many states prohibit the shipment with the body of articles that may have been exposed to contagion during the course of a contagious disease. Persons who have been exposed to such diseases may not accompany the dead body under the rules of certain states.

BURIAL

The usual method of final disposal of the dead human body, other than the methods prescribed by anatomical acts in the case of unclaimed dead, is burial. Under the common law it would probably be legal to bury a body in any place determined on by the next of kin, on whom the duty of sepulture devolves. The right of burial in a place requested by the deceased or determined on by the next of kin would no doubt be restricted, even under the common law, by regard for public health and public sentiment. The legality of interment in places other than recognized burial grounds has usually come to the attention of the courts in the case of infants and children who have been buried by parents who claimed that they could not meet the expense of regular burial or that the recognized burial place was inaccessible. Questions other than burial, such as infanticide or failure to have filed a certificate of death, may enter into such cases.

What might be legally done under the common law is restricted by the statutory regulations in force in all states relative to the disposal of the dead. What may be done is influenced first of all by the necessity of filing a death certificate signed by the attending physician or by the health officer, registrar of vital statistics, coroner or medical examiner if death occurred without medical attendance. Filing of the

certificate of death necessitates the obtaining of a burial, disposal or removal permit. The regulations concerning the latter usually specify the length of time that the body may remain unburied and the place and manner of its interment.

CREMATION

Cremation is one of the most ancient forms of disposal of the dead. With the advent of the Christian era it fell into disuse, to come into favor again only comparatively recently. The paucity of definite regulations relating to this form of disposal is ascribed to its relatively recent revival. In general, it would appear that if there are no definite legal provisions regulating the procedure, conformity with the regulations for burial will permit cremation.

California, Colorado and Pennsylvania by statute require special permits for cremation. Connecticut, Missouri, New Jersey and Ohio have regulations relating more especially to the location and management of crematories, the records to be kept or the disposition that may be made of the ashes. Minnesota, New York and Nevada have statutes that make burial and cremation alternative methods of disposal. Although these are the only states mentioned as having regulations regarding cremation, in many other states the permission of the coroner or medical examiner is necessary before a body may be cremated. The purpose of such a rule is the wise one of preventing the destruction of necessary evidence if circumstances should make necessary an inquest or an investigation of the death.

The brief section on cremation closes with the following interesting paragraph ¹⁵

Whether special regulations concerning cremation exist in a given jurisdiction or not, it is essential, when cremations are made, to secure the burial permit, etc. Even when a physician cremates the body of a stillborn child, when it has advanced to that stage of development when it can be said to be a human body, or when he burns a portion of a body removed during the course of operation (if that portion of a body is considered as a dead body in his particular jurisdiction), it is essential that all certificates be filed, permits obtained, and returns and reports be filed as required by law in case of interment, if no specific regulation concerning cremation exists.

EXHUMATION

Most of the common law court decisions on the subject of exhumation relate to controversies between surviving relatives over the removal of a body that has been buried. Exhumation in such cases has no medicolegal interest. Such an interest is involved, however, if the exhumation is for the purpose of determining the cause of death in

¹⁵ Weinmann (footnote 2 p 178)

order to establish or to disprove a claim for insurance. Courts usually refuse to order exhumation unless some controlling public reason or superior private right is involved.

But the matter of exhumation is not entirely one of common law. In many states it is covered by statute or by the regulations of the department of health. The coroner or medical examiner may authorize exhumation, if there have come to light after the burial of the body, circumstances that make examination of the body advisable from the standpoint of criminal justice.

The statutory or departmental regulations of most states in regard to exhumation have for their chief purpose the protection of the public health. With this object in view, the rules laid down relate to the time of day or year when exhumation may be done, or they prohibit the presence of any persons other than those necessary for the work. Some states require a special permit from the department of health, the department of public welfare or the bureau of vital statistics. Some require special permits for disinterment only when death was due to certain specified infectious diseases. In such cases there may be prescribed a minimum period of time that must elapse between death and exhumation.

The subject of exhumation is briefly summarized by Weinmann thus ¹⁶

Although courts are loath to disturb a corpse in its final resting place, yet exhumation will be ordered when required by the demands of justice and equity. In all such cases, however, there must be a strong showing of some controlling public reason or superior private right, and due regard will always be given to the wishes of the decedent expressed during his lifetime, when possible, to considerations of public sentiment, public health, and public welfare, generally, and finally, to the feelings of surviving relatives and friends.

CONCLUSION

An attempt has been made to summarize the information contained in "A Survey of the Law Concerning Dead Human Bodies." For most of the subjects covered, the original bulletin quotes in detail the laws of the various jurisdictions, which are arranged alphabetically according to states and territories. The reader who desires more detailed information of the law on any particular subject in any given jurisdiction is referred to the original. It should be borne in mind that the laws as given may be modified by additional local municipal regulations.

¹⁶ Weinmann (footnote 2, p. 192)

Notes and News

University News, Promotions, Resignations, Appointments, Deaths—The University of Pennsylvania has conferred the honorary degree of doctor of laws on Theobald Smith, who recently retired as director of the department of animal pathology at Princeton of the Rockefeller Institute for Medical Research.

Matthias Nicoll, Jr., has resigned as commissioner of health for the state of New York to become health officer of Westchester County, N. Y.

Thomas Parran, Jr., of the U. S. Public Health Service has been appointed commissioner of health for the state of New York.

Viktor Muller-Hess, professor of legal and social medicine in the University of Bonn, has been appointed professor of legal medicine in the University of Berlin in the place of Fritz Strassmann.

Dr. Kenneth M. Lynch, professor of pathology, Medical College of the State of South Carolina, was elected president of the South Carolina Medical Association at its eighty-second annual convention, May 6 to 8. Dr. Lynch is also serving this year as president of the American Society of Tropical Medicine and as president-elect of the American Society of Clinical Pathologists.

Medical Fellowship Board of National Research Council—The next meeting of this board will be held on Oct. 14, 1930. Applications for consideration at this meeting must be in the hands of the secretary of the board (B and 21st Streets, Washington, D. C.) before September first next.

Charles Nicolle, director of the Pasteur Institute of Tunis, and well known for his work on typhus fever for which he was awarded a Nobel Prize in 1928 has been elected a member of the French Academy of Sciences.

At the recent meeting in Atlantic City of the Association of American Physicians, the Kober Medal was awarded to James B. Herrick, Chicago, for his investigations in clinical medicine.

George R. Minot, Boston, has been awarded a gold medal by the National Institute of Social Sciences, New York.

The Trudeau Medal of the National Tuberculosis Association has been awarded to Henry Sewall, Denver, in recognition of his work on tuberculosis.

H. J. B. Fry, pathologist to the Research Institute, Cancer Hospital, London, died on May 5, 1930, from streptococcal infection contracted while making a postmortem examination.

American Association of Pathologists and Bacteriologists—At the meeting in New York, April 17 and 18, 1930, the following officers were elected: president, George R. Callender, vice-president, Ward J. MacNeal, treasurer, F. B. Mallory, secretary, Howard T. Karsner, incoming member of council, O. T. Avery, assistant secretary, Robert A. Moore.

For distinguished service in pathology and bacteriology, the Gold Headed Cane of the Association was conferred upon Theobald Smith, Princeton, N. J.

Committee on Research in Syphilis—It is reported (Venereal Disease Information 11:63, 1930) that this committee now sponsors four major groups of studies: the biology of *Spirochaeta pallida* (cultivation, life cycles, different strains, relation between syphilis and yaws), the reaction of the body to syphilitic infection (latent infection, reaction to infection and to antisymphilitic drugs, mechanism of Kahn and Hinton tests), experimental chemotherapy, relation of treatment to the development of dementia paralytica. For these purposes, twenty grants have been made, amounting in all to \$91,515. In addition, funds have been provided for the study of the results of treatment for syphilis, and for other special objects.

German Society for Legal and Social Medicine—The society has a membership of about 400 and publishes the *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*.

International Congress of Veterinary Medicine—The Eleventh International Congress on Veterinary Medicine will be held in London, England, Aug. 4 to 9, 1930. The General secretary is F. Bullock, LL.D., F.C.I.S., 10 Red Lion Square, London, W. C. 1.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE R-T INTERVAL IN MYOCARDIAL INFARCTION A R BARNES and M B WHITTEN, *Am Heart J* **5** 142, 1929

In the left ventricle the branches of both the right and the left coronary arteries are similar in architecture, leaving the main artery at right angles and directly penetrating the myocardium. In the right ventricle the branches of the right coronary artery leave it in the same general direction as that of the vessel from which they arise. Myocardial infarction of the right ventricle is rare. Infarction from occlusion in the right coronary circuit is almost always found in the posterior portion of the left ventricle and septum, and at times in the apex. Occlusion of the left coronary artery usually involves some part of the anterior portion of the left ventricle and septum. Infarcts in these various locations produce characteristic changes in the R-T interval, which enable one not only to localize the region involved but also often to identify the coronary artery that is the seat of the trouble.

PEARL ZFEK

THE AGE AND SEX INCIDENCE OF ARTERIAL HYPERTENSION J E F RISEMAN and SOMA WEISS, *Am Heart J* **5** 172, 1929

The curve of age incidence in patients with hypertension shows a gradual progressive rise up to the age at which begins the involution of the male and female glands of internal secretion. At this point there is a sharp sudden rise. More than 60 per cent of the cases occur in patients between the ages of 45 and 69. These facts suggest the possibility of an etiologic relationship between involutional changes of the human body and hypertension.

PEARL ZEEK

LYMPHATIC ABSORPTION OF PARTICULATE MATTER THROUGH THE NORMAL AND THE PARALYZED DIAPHRAGM W S LEMON and G M HIGGINS, *Am J M Sc* **178** 536, 1929

Experiments on absorption through the normal and the paralyzed diaphragm confirm the observations made by Higgins and Graham that five main channels carry particulate matter from the peritoneum upward through the thorax and into the blood stream. The experiments also demonstrate the presence of a descending thoracic vessel which passes downward over the posterior wall of the thorax, sometimes receiving tributaries from the vessels of the posterior portion of the diaphragm and communicating with the lymph nodes in the region of the kidney. The particulate matter seems to be taken up diffusely on the under surface of the diaphragm. The transfer from the peritoneal surface to the pleural surface is rapid, and the penetration of particulate matter into the blood stream is effected within a period of from thirty minutes to one and a half hours. The material taken from the lymphatic vessels on the surface of the diaphragm is mainly found in a free state, although a small amount is in phagocytic cells. That taken from the lymph nodes is found mainly in phagocytic cells, although a slight amount is still in a free state. When obtained from the blood the material is both in a free state and within phagocytic cells. It is probable that the monocytes take up the free material quickly after it has been passed into the blood stream. There is no question but that normal muscular contraction of the diaphragm contributes much to the passage of the particulate matter. Nevertheless the difference in size of the lymphatics on the two leaves of the diaphragm is

also important. The lymphatics on the right side are much larger and carry a much greater proportion of the lymphatic flow than those on the left. Even after paralysis of the right half of the diaphragm, the pattern discovered following the lapse of thirty minutes is more distinct than on the normal left side. Absorption through the left half when it is paralyzed is insignificant.

JOHN PHAIR

INTRACRANIAL PRESSURE IN MAN DURING SLEEP AND UNDER CERTAIN OTHER CONDITIONS. LEWIS STEVENSON, B. E. CHRISTIANSEN and S. BERNARD WORTIS, *Am J M Sc* **178** 663, 1929

1 Intracranial pressure is increased during sleep. The pressure gradually rises until the patient is sound asleep, when the curve reaches its maximum, this is maintained at a fairly constant level during sound sleep. On awakening, the pressure falls rather rapidly again to normal.

2 There is an increase of the intracranial pressure on lying down.

3 Partial sleep or drowsy states are associated with a rhythmic increase of the intracranial pressure which is not so high as during sound sleep.

4 Certain drugs which are known to affect the nervous system as sedatives or as stimulants depend in part for their effect on a hitherto unappreciated mechanical factor, namely, an increase or a decrease of the intracranial pressure. For example, morphine, a sedative, causes an increase of the intracranial pressure, while caffeine, a stimulant, produces a fall.

5 The intracranial pressure is, within wide limits, independent of the blood pressure.

6 The authors' conception of the physiology of sleep, arrived at from a study of their experiments and those of other workers, is as follows.

They believe that the sympathetic center in the brain which maintains vasomotor tone in the vessels becomes periodically fatigued. This results in a vasodilatation of the blood vessels of the brain, as well as those of the periphery. Accompanying this, as further evidence of fatigue in the sympathetic system during sleep, are the constricted pupil, the slower heart rate and the decrease of blood pressure. This vasodilatation in the brain would result in one of two things.

1 The brain volume would be increased with a consequent pulling apart of the neurons (diaschisis). This might result in a physiologic interruption of function in the manner suggested by Cajal and Duval when they assumed that the dendrites of the nerve cell were contractile.

2 The pressure of the cerebrospinal fluid within the brain would be increased and especially in the pericellular spaces, thus altering the conductivity of the synapse.

AUTHORS' SUMMARY

DIABETES INSIPIDUS AND LESIONS OF THE MIDBRAIN. T. B. FUTCHER, *Am J M Sc* **178** 837, 1929

A case of diabetes insipidus due to an alveolar carcinoma of the hypothalamus, secondary to a primary carcinoma of the lung, and without involvement of the pituitary, is reported. The case would naturally tend to support the view held by many that the diabetes insipidus is due to disturbance of certain regulatory centers in the hypothalamus. The studies supporting the pituitary and hypothalamic conception of the origin of the disease are reviewed. Reference is made to the fact that it now seems amply demonstrated that there are definite nerve fibers connecting the tuber cinereum and the posterior lobe of the hypophysis. The belief is expressed that, although there may be certain centers in the hypothalamus regulating water exchange in the body, the evidence seems strong that disturbance of the action of a diuretic-antidiuretic hormone produced in the posterior lobe of the pituitary is an important factor in the etiology of the disease, possibly by sensitizing these centers or by influencing their function.

AUTHORS' SUMMARY

MECHANISM OF OVULATION IN THE RABBIT M H FRIEDMAN, Am J Physiol
90 617, 1929

While no effect was observed on ovulation in the rabbit by the transplantation or injection of rat hypophysis, the intraperitoneal injection of the urine of pregnant women produced luteinization of the corpora hemorrhagica of the ovary of the rabbit, and a single injection provoked ovulation. Urine from nonpregnant women was without this effect.

H E EGGERS

PRODUCTION OF ARTIFICIAL DECIDUOMA WITH EXTRACTS OF THE CORPUS LUTEUM
L A GOLDSTEIN and A J TATELBAUM, Am J Physiol **91** 14, 1929

The writers' experiments confirm the observation that in corpus luteum extract there is a special hormone which as one of its functions, so sensitizes the uterine mucosa in the guinea-pig that deciduoma is formed on indifferent stimulation of the endometrium at the proper period of the sexual cycle.

H E EGGERS

THE EYE IN DIABETES MELLITUS MARTIN COHEN, Arch Ophth **2** 529, 1929

Diabetes usually occurs in middle life when arteriosclerosis is apt to be present. But the ocular complications appear after the disease has continued for some years, and the patient is debilitated, susceptible to infections, or chronic disorders have set in. Of all eye lesions associated with diabetes, the incidence of retinitis is highest, cataract, chronic retrobulbar neuritis, muscular disorders and disturbances of accommodation, refraction and iritis occur more rarely.

The structure of the eye most frequently involved in diabetes is the retina, primarily its vessels, the most typical example being lipemia retinalis, which involves both eyes and occurs in severe diabetes. In a case cited, all the retinal blood vessels were moderately dilated and had a milky appearance. This appearance alone, exclusive of any examination of blood or urine, determines the diagnosis of diabetes. Microscopically, the vascular walls were not involved in any case reported. This appearance of the fundus antedates coma by six weeks. The author believes that the appearance of lipemia retinalis is closely related to the total fat content of the blood rather than to the cholesterol.

Diabetic retinitis is usually bilateral. The retinal vessels often show definite pathologic evidence with varying degrees of arteriosclerosis. If general hypertension is present, it is apt to aggravate the lesion of the fundus. The author believes that this lesion is mainly due to sclerosis of the retinal vessels, which may be either mild or severe. The disturbed sugar metabolism is only contributory.

Cataract in young diabetic patients may exist from early childhood. In older persons it is probably the usual type of senile cataract complicating diabetes. Diabetic and senile cataracts cannot be differentiated by any known test. The author cites an instance of diabetic cataract developing in a child at the age of 1 year and 1 month.

In experiments with lenses of oxen, it is found that the fresh lens, when immersed in Ringer's solution and incubated, develops the power to convert dextrose into lactic acid. The same utilization occurs when the lenses are immersed in the aqueous humor, but there is no change if placed in the vitreous humor. This ability to utilize dextrose is apparently dependent on the presence of glutathione in the lens. In the diabetic person, the production of cataracts may be an expression of the general inability to utilize dextrose, and the lens therefore degenerates.

CHARLES WEISS

THE REACTIONS OF SIMPLE GOITRE TO IODINE BRUCE WEBSTER, Bull Johns
Hopkins Hosp **45** 215, 1929

Potassium iodide in quantities of 5, 25 and 125 mg was injected intraperitoneally into rabbits with simple hyperplastic thyroid glands. The changes

in heat production were studied and correlated with the histologic changes produced in the gland, as determined by biopsy. The quantity of thyroid hormone elaborated, as indicated by changes in heat production, appeared to vary directly, within certain limits with the amount of available iodine, as did the extent of involution produced in the gland. This relationship apparently held true until involution was nearly complete.

AUTHOR'S SUMMARY

THE COLOR OF THE SKIN IS ANALYZED BY SPECTROPHOTOMETRIC METHODS
C SHEARD and LOUIS A. BRUNSTING, *J Clin Investigation* 7:559-575, 593, 1929

The fundamental hue or dominant wavelength of the skin lies in the spectral region 590 millimicrons (sodium yellow). The deposition of melanin in the skin from sunlight decreases its relative luminosity but does not disturb the hue or its purity. The same hue prevails in the white as in the so-called black, red and yellow races. The blood in the superficial capillaries exerts a major influence on the color of the skin.

CHANGES OF THE TRYPA NOCIDAL PROPERTY OF SERUM IN PERNICIOUS ANEMIA
F ROSENTHAL, *Klin Wchnschr* 8 1436, 1929

During periods of remission the trypanocidal property of the serum of patients with pernicious anemia diminishes. It increases with the return to normal of the blood. There is no satisfactory explanation for these changes, although they resemble those occurring in diffuse diseases of the liver.

EDWIN F. HIRSCH

THE RESORPTIVE PROPERTY OF THE INTESTINAL WALL FOR H AND OH IONS
K SCHEER, *Klin Wchnschr* 8 1757, 1929

About two hours after rectal injection of hydrochloric acid the urine becomes distinctly more acid, and about four hours after the rectal injection of sodium bicarbonate the urine becomes distinctly more alkaline. These results demonstrate that the mucosa of the colon is able to absorb H and OH ions.

EDWIN F. HIRSCH

THE EFFECT OF AN EXTRACT OF THE ANTERIOR LOBE OF THE HYPOPHYSIS ON THE EXCRETION OF MILK
F GRUTER and P. STRICKER, *Klin Wchnschr* 8 2322, 1929

A hormone of the anterior lobe of the hypophysis has a stimulating effect on the mammary glands. Probably at the time of birth it stimulates the secretion of milk. Extracts from the liver, the lungs, the posterior lobe of the hypophysis and even the placenta are without such effects.

AUTHORS' SUMMARY

EFFECT OF NUTRITION ON THE BEGINNING OF PUBERTY AND THE OVARIAN CYCLE
W. NEUWEILER, *Ztschr f Geburtsh u Gynak* 94 28, 1928

The date of the first estrum and the subsequent ovarian cycle of young female rats fed from the third week of life with different diets was determined by the method of Allen and Doisy. The diets used were normal, rich in carbohydrates, rich in proteins, rich in fats, free from vitamins plus factor A, B, C, and E, respectively. With the normal diet, the first estrum appeared after from forty-two to forty-five days, and the normal ovarian cycle was from four to seven days. With all the other diets used the animals could not be kept alive over a long period. All the animals of these groups were dead after one hundred and fifteen days. Degenerative changes of the sexual organs appeared in these animals at an earlier date than noticeable changes in their general status. No estrum was

seen in the great majority of animals fed with diets rich in fats or free from vitamins. In animals fed with the remaining diets, the beginning of the estrum was delayed for from one to three weeks. The ovarian cycle in animals fed with a diet rich in carbohydrates was from two to three weeks, in those with a diet rich in proteins, from twenty-two to twenty-four days. A second estrum, however, appeared in only a few of these animals. The diet free from vitamins plus factor A had a similar effect. Animals fed with diets free from vitamins plus factors B, C and E, respectively, had a delay of fourteen days of the first estrum. This condition then remained permanent either immediately following the first estrum (vitamin E), after a period of five days (vitamin C) or after fifteen days (vitamin B). The ovaries of all animals fed with pathologic diets showed a marked hypoplasia and severe degeneration of the follicles.

W C HUEPER

PATHOGENESIS OF ICTERUS NEONATORUM W G SCHULTZ, *Ztschr f Geburtsh u Gynak* **94** 793, 1929

Erythrophagocytosis and considerable deposition of iron pigment in the reticulo-endothelial system of the spleen and liver are absent in fetuses until 4 or 6 months of age. They are present in mature and immature fetuses during delivery and increase in amount with the duration of the delivery and of the extra-uterine life. The common icterus neonatorum is considered as an expression of a hyperfunction of the reticulo-endothelial system. The cause of it is unknown.

W C HUEPER

Pathologic Anatomy

CONGENITAL HEART DISEASE WINSTON F HARRISON, *Am Heart J* **5** 213, 1929

A clinicopathologic study was made of a case of congenital heart disease exhibiting the complex known as the "tetralogy of Fallot," on which was superimposed a subacute bacterial endocarditis with massive vegetations involving chiefly the tricuspid valve. Associated anomalies in both the heart itself (Chiari's network) and elsewhere are discussed with reference to their bearing on the theories of the etiology and pathogenesis of congenital cardiac defects. Special reference is made to the collateral pulmonary circulation in the presence of extreme pulmonary stenosis or atresia when the ductus arteriosus is closed. In such cases the enlarged bronchial arteries usually supply the blood to the lungs, although sometimes the pericardials, mediastinals, coronaries, esophageals, subclavians or other arteries are called on to assume this function. In the present case the bronchial arteries were greatly enlarged. Aspects of the pathologic physiology are discussed with reference to the degree of disturbance of the circulation and its relationship to prognosis. The danger from infections is noted particularly in the extraordinary forms of vegetative endocarditis to which such cases are especially prone. Most patients die from intercurrent diseases and not from cardiac failure.

AUTHOR'S SUMMARY

PROGERIA REVIEW OF THE LITERATURE WITH REPORT OF CASE VINCENT T CURTIN and HERMAN F KOTZEN, *Am J Dis Child* **38** 993, 1929

We have presented a case of what we believe to be a relatively rare disease. The possibility that this condition should be considered as scleroderma has been suggested. The characteristic facies, evident from a comparison of the photographs and commented on by Gilford and other observers, the changes in the cardiovascular and osseous systems, the similarity in the mentality of the persons affected, the subsequent course and termination, and the pathologic observations

in the cases coming to autopsy, seem sufficient to warrant its description as something more than dermatosclerosis. Neither can it be considered Still's disease, as the arthritis is but one of the many clinical manifestations. Whether or not we accept Gilford's name, progeria, or that of dwarfism of the senile type, proposed by Variot and Pironneau, we must certainly admit this morbid state to be a distinct entity. Failure to secure permission for a postmortem examination in the case of L. F. places any opinion as to the possible cause in the realm of speculation, although we feel that the arguments in favor of disease of the suprarenal gland have the most foundation in fact. Until more of these cases come to autopsy, however, we must remain in doubt as to the causative factor of what is clearly a most interesting disease.

AUTHORS' SUMMARY

INTERPRETATION OF ROENTGENOGRAMS OF THE CHEST IN CHILDREN BASED ON OBSERVATION AT NECROPSY. TUBERCULOSIS. JOHN A. BIGLER, *Am J Dis Child* **38** 1166, 1929

Evidence of tuberculosis is not found pathologically as frequently as one would expect from the diagnosis of films of the chest. The incidence of tuberculosis in children admitted to the Children's Memorial Hospital is much lower than the figures quoted for tuberculosis in children. The primary focus is found more often pathologically than on the x-ray film, unless calcification is present. The more or less characteristic hilar, or mediastinal shadow, is the most frequent guide to the diagnosis. Miliary tuberculosis can be recognized on the films in only about 50 per cent of the cases. It can be differentiated from chronic tuberculous bronchopneumonia by the smaller size of the shadows. Repeated tuberculin tests, when negative, are important in ruling out a diagnosis of tuberculosis.

AUTHOR'S SUMMARY

ANOMALIES OF THE URINARY TRACT IN INFANTS. ALGERNON S. HURT, JR., *Am J Dis Child* **38** 1202, 1929

In a series of 101 necropsies on infants less than 2 weeks of age five cases were found in which there were anomalies of the urinary tract. Since these anomalies occurred in such a low age group, this percentage may be taken as at least an indication of the incidence of anomalies of the urinary tract at birth. Although the series reported is comparatively small, the data corroborate the evidence that anomalies of the urinary tract are by no means infrequent in infants and children.

AUTHOR'S SUMMARY

SPLENOMEGALY. PORTAL PHLEBOSCLEROSIS. SAMPSON J. WILSON and MAX LEDERER, *Am J Dis Child* **38** 1231, 1929

A case of portal phlebrosclerosis in a boy, aged 2 years, due to a congenital stenosis, is described.

CONGENITAL ESSENTIAL THROMBOCYTOPENIA. HARRY M. GREENWALD and IRVING SHERMAN, *Am J Dis Child* **38** 1245, 1929

A case of congenital thrombocytopenic purpura is reported. The reduction in the number of the platelets is attributed to an insufficiency of megakaryocytes of the bone-marrow. The coincidence of anomalies of the heart and of the thymus gland with defective formation of the megakaryocytes supports the conception of the congenital nature of the thrombocytopenic purpura.

AUTHORS' SUMMARY

MIKULICZ'S DISEASE AND THE MIKULICZ SYNDROME. J. P. CROZER GRIFFITH, *Am J M Sc* **178** 853, 1929

Two cases of Mikulicz' syndrome are reported, one dependent on leukemia, the other, which might be called Mikulicz' disease proper, having no discoverable

cause The symptoms and lesions are discussed with special reference to the influence of tuberculosis A study of some of the literature as well as the bioscopic examination in my own case supports the conclusions of others, viz, that although tuberculosis may be a cause of Mikulicz' disease, it is rarely so, and that even a histologic appearance in the glands which strongly suggest tuberculosis is not a positive proof that the disease is present

AUTHOR'S SUMMARY

THE FINER HISTOLOGY OF THE NORMAL GLOMERULUS LEONE MCGREGOR,
Am J Path 5 545, 1929

The following conclusions have been reached after studying oil immersion fields of tissues stained as described previously The glomerular, capsular and tubular basement membranes are continuous and stain red with van Gieson, blue with Ohmori and dark blue with Mallory-Heidenhain azan-carmine The capsule and tubules have an additional external, reticular, argyrophil covering The glomerular basement membrane is thinner than that of the capsule and tubules Pores have not been demonstrated, nor any elastic fiber content The glomerular, capsular and tubular epithelium is continuous The glomerular epithelial cells have abundant cytoplasm and large vesicular nuclei with one or more prominent nucleoli These are only cells which lie outside the glomerular basement membrane They form complete covering for the loops following closely both tips and crevices They are arranged in a single layer and not in a syncytium The glomerular endothelium lies inside the basement membrane and therefore cannot be confused with epithelium The cytoplasm is very small in amount and the nuclei have a thick nuclear membrane enclosing much coarse chromatin Endothelial cells are much less numerous than epithelial There are cells, probably endothelial, which lie inside the glomerular basement membrane but are partially surrounded by it Their nuclei seem to be identical with those of typical endothelium and they have very little cytoplasm Their situation at the orifices between the loops makes examination very difficult Further study to decide their nature is in progress Connective tissue cells and reticulum fibrils pass in at the hilus accompanying the vas afferens until it subdivides near the center of the glomerulus

AUTHOR'S SUMMARY

THE CYTOLOGICAL CHANGES OCCURRING IN THE GLOMERULUS OF CLINICAL GLOMERULONEPHRITIS LEONE MCGREGOR, Am J Path 5 559, 1929

From a microscopic study of glomeruli of sixty cases of acute and chronic glomerulonephritis the conclusions are as follows The intracapillary cellular increase is chiefly endothelial and is explained by the numerous mitoses The leukocytes are polymorphonuclear and are much less numerous than the endothelial cells A small amount of fibrin and debris is found in most of the capillaries The extracapillary changes consist of proliferation, degeneration and desquamation of glomerular and capsular epithelium These are easily distinguished from intracapillary lesions because the glomerular basement membrane lies between Crescent formation may be due to capsular epithelial proliferation or to a combination of capsular proliferation and glomerular epithelial desquamation In a very early period, hyaline fibers appear between the cells and are soon continuous with the capsular basement membrane Hyaline fibers also appear inside the glomerular capillaries They stain blue with the Mallory-Heidenhain azan-carmine, or with Ohmori's rein blau and not at all with silver When first formed, they lie between the proliferating endothelial cells and are usually attached to the basement membrane They appear as fine sharp lines with knobs at intersections They soon form a definite meshwork enclosing the intracapillary cells This fibrous meshwork is believed to be an important and typical finding in glomerulonephritis It is the initial stage of the hyalinization of the glomerulus The process takes place in all the glomeruli but not always to the same degree When the loops are only partially occluded, blood continues to circulate along one side and the

glomerulus has some function. When every loop is occluded, the circulation cannot continue. The fibers within the loop increase in number and caliber, many fuse, and the enclosed cells are atrophied by pressure. The glomerular loop arrives at a stage where it consists of a few flattened epithelial cells, a basement membrane and a lumen completely filled with a hyaline fibrous mass enclosing a few nuclei. Adjacent loops fuse, and the fibers contract. The glomerular epithelial atrophies and disappears. At the same time the fibers of the crescent have increased and contracted until they have eliminated most of the cells. The fibrous crescent now fuses with the fibrous glomerulus. The end-result is a sphere of fibrous connective tissue containing practically no nuclei. The origin and composition of the intracapillary hyaline fibers are undetermined and require further study. They do not seem to be fibrin or derivatives of it. They are thought to be a crystallization or precipitation of the intercellular exudate under the influence of the proliferating endothelial cells or perhaps a product of the glomerular basement membrane. Later they are indistinguishable from typical collagenous fibers. The foregoing processes are typical of clinical glomerulonephritis. The finding of a glomerular cellular increase (usually monocytes) following pneumonia and other infections is not to be confused with clinical nephritis. The nonclinical cases do not have the characteristic intracapillary fibrous meshwork.

AUTHOR'S SUMMARY

LIPOID NEPHROSIS E. T. BELL, *Am J Path* 5 587, 1929

A survey of the recent literature shows a tendency to use "lipoid nephrosis" in a broad way to include all cases of nephritis with edema, albuminuria, normal blood pressure and normal blood nitrogen. This clinical definition includes many cases that are anatomically acute or mild chronic glomerulonephritis. All the clinical phenomena of lipoid nephrosis, viz., albuminuria, edema, normal blood pressure, hypercholesterolemia, decrease of the plasma proteins with reversal of the albumin globulin ratio and normal blood nitrogen, may occur in a less pronounced form in glomerulonephritis. There are many transition cases between lipoid nephrosis and glomerulonephritis, viz., those that fit the definition of lipoid nephrosis except for the presence of hypertension or moderate nitrogen retention. These are called the mixed type, or nephritis with a nephrotic Emschlag. From the clinical standpoint the two diseases cannot be sharply separated. A histologic study has been made of 10 cases of large, fatty kidneys, without tubular atrophy, that were clinically nephritis. Four of these are classed as pure lipoid nephrosis, 3 as nephritis with nephrotic Emschlag (mixed type) and 3 of uncertain type because of lack of clinical data. The glomeruli are not normal in any instance, but the lesions are not of uniform type. In pure lipoid nephrosis there is a varying increase in the number and size of the glomerular endothelial cells and an uneven thickening of the basement membrane. In the mixed type (nephritis with nephrotic Emschlag) there is a marked thickening of the basement membrane. In one instance the capillaries were compressed by enlarged epithelial cells. In two instances there was a definite increase in the number and size of the glomerular endothelial cells, and a few areas in the glomeruli showed the changes characteristic of typical clinical glomerulonephritis, i. e., capillaries filled with endothelial cells and a network of hyaline fibers. Three large noncontracted kidneys were studied in which the data were insufficient to determine whether they should be classed as lipoid nephrosis. Two of these showed extreme thickening of the basement membrane. The third showed an enormous accumulation of fat in the tubules and glomeruli, large glomerular epithelial cells with hyaline and fatty degeneration, and leukocytes and hyaline fibers within the capillaries as in glomerulonephritis. Lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially obstructed so that they continue to function and tubular atrophy does not occur.

AUTHOR'S SUMMARY

OBSTRUCTIVE CIRRHOSIS H E MACMAHON and F B MALLORY, *Am J Path* 5 645, 1929

This paper is based on the study of thirty cases of uncomplicated obstructive cirrhosis, ten in infants and twenty in adults averaging about 60 years of age. The common cause in infancy is a congenital malformation of the bile duct, whereas in the adult it results from tumors, concretions and inflammatory strictures. The gross and microscopic observations of obstructive cirrhosis are described, and in addition, reference is made to a few of its more important clinical features.

AUTHORS' SUMMARY

HEMORRHAGES IN THE FUNDUS IN HYPERTENSION FRITZ LANGE, *Arch Ophth* 2 551, 1929

With the recently established differential diagnosis of arteriosclerosis and hypertension, it becomes necessary to refer hemorrhages in the eye to their proper cause. Hemorrhages may occur anywhere in the retina. Of sixty patients examined fifty-seven had high blood pressure (from 160 to 200 + mm of hydrogen). In fifteen of these there was only hypertension without arteriosclerosis, and these showed characteristic changes in the arteries of the fundus, as to caliber and tortuosity. The other forty patients showed clinical signs of arteriosclerosis, the average age being higher than that of the pure hypertensions. No case of pure arteriosclerosis was found. In advanced cases of arteriosclerosis and hypertension the blood vessels of the fundus were changed in the same way, and as frequently as in pure hypertension, differentiation as to origin could not be made. The blood vessels show imbibitions of calcium and cholesterol in about 10 per cent of the arteriosclerotic cases, corresponding to the degree of clinical arteriosclerosis. For controls, patients with clinically pure arteriosclerosis and low blood pressure were examined, and each patient was found to be free of retinal hemorrhage. Only three of the sixty patients with retinal hemorrhage did not show hypertension, and in these the etiology was obscure, certainly it was not due to arteriosclerosis. Retinal hemorrhages in cases of diabetes and syphilis were found in conjunction with high blood pressure with but few exceptions. No cases of cerebral apoplexy without hypertension were found, unless the hypertension was masked by cardiac insufficiency. The same factors are responsible for retinal hemorrhage as for cerebral apoplexy, and both usually originate in the capillaries.

CHARLES WEISS

PAPILLARY CYSTADENOMA LYMPHOMATOSUM (TERATOID IN PAROTID REGION)
ALFRED SCOTT WARTHIN, *J Cancer Research* 13.116, 1929

The author reports, in great detail, two identical tumors which he found among "diagnostic material of several hundred thousand cases examined by him since 1895." He states that he could find no record in the literature of the existence of a similar blastoma. He designates the new growth as a "papilliferous cystadenoma lymphomatosum" which he regards as a very rare teratoid of the parotid gland region. It represents a heterotopia or dystopia of pharyngeal entoderm, resembling in structure most closely, the mucosa of the cartilaginous portion of the eustachian tube.

B M FRIED

HISTOLOGICAL FINDINGS IN HEARTS WHICH HAVE BEEN EXPOSED TO RADIATION IN THE COURSE OF TREATMENT OF ADJACENT ORGANS A A THIBAUDEAU and W L MATTICK, *J Cancer Research* 13 251, 1929

The authors have selected for their study ten hearts secured at autopsy from patients in whom extensive radiation had been applied in the precordial region during the course of treatment of malignant condition of the heart. It appeared to them that radiation of the human heart as applied in the treatment of malignant neoplasm in its immediate vicinity may cause definite injury to the cardiac muscle.

The pathologic process varies from slight interstitial fibrosis to hyaline and fatty degeneration of the muscle fibers with necrosis

B M FRIED

CHOLESTEROSIS OF THE GALLBLADDER C F W ILLINGWORTH, Brit J Surg **17** 203, 1929

Of thirty-five cases of operation for disease of the gallbladder, twenty-one showed evidences of cholesterosis. The deposition of lipoids may be diffuse, patchy or polypoid as bright yellow areas located on the ridges of the mucosa which stand out distinctly against the surrounding red mucosa. The organ otherwise may appear grossly normal but more frequently it is thickened. The lipoids are situated in the mucous coat but occasionally in the fibromuscular layers, and the villi may be distended by foamy cells in the stroma. The bile was usually sterile, thick and tarry, but was clear and contained from 503 to 907 mg per cent as compared to a normal determination of 329.

RICHARD A LIFVENDAHL

ENDOTHELIOMA OF THE NASOPHARYNX A J GARDHAM, Brit J Surg **17** 242, 1929

This study covers nine cases. On the basis of clinical manifestations, the new growth is thought to have its origin in close relation to the eustachian tube, pharyngeal wall and fifth nerve. In the nasopharynx it appears as a firm, pink small and sessile tumor in the region of the eustachian tube and tends to spread underneath the mucous membrane of the mouth, after involving the soft and hard palates. Further extension may occur to the base of the skull and ultimately may involve the outer surface of the cranium. In the course of this extension, the sensory and motor divisions of the fifth nerve, the sixth nerve—as the results of tumor invasion of the carotid canal or the sphenoidal sinus—and lastly the nerves of the palate may all be involved, resulting in symptoms referable to these structures. More rarely, however, any one of the cranial nerves may be affected by the neoplasm. Secondary deposits in the cervical lymph glands, on both sides of the neck, may occur before the primary growth is large enough to produce symptoms. The glands are hard, fixed and discrete and show no tendency to break down. Microscopically, the primary and secondary growths consist of large and irregular but mostly spheroidal cells, arranged in groups in a tubular fashion separated by connective tissue.

RICHARD A LIFVENDAHL

ANEURYSM OF THE SPLENIC ARTERY W ANDERSON and JOHN GRAY, Brit J Surg **17** 267, 1929

Degeneration and necrosis of the media of the splenic artery led to the formation of the saccular aneurysm and secondary extensive and fatal intraperitoneal hemorrhage. A review of fifty-eight collected instances did not show an outstanding causative factor, but in some septic embolism, arteriosclerosis and syphilis have been suggested.

RICHARD A LIFVENDAHL

PRIMARY JEJUNAL ULCER J M BLACK, Brit J Surg **17** 338, 1929

A minute perforation surrounded by an acute inflammatory tract was found 2 feet distal to the commencement of the jejunum. Ulcers in this location are rare except following gastrojejunostomy. In this case there were no evidences of typhoid fever nor was there any history of trauma to the abdomen.

RICHARD A LIFVENDAHL

PATHOLOGIC GRANULATION OF FINELY GRANULATED LEUKOCYTES H. MOMMSEN,
Klin Wchnschr **8** 2420, 1929

With a Giemsa stain at pH 5.4, the normal finely granular leukocytes are without granules, while pathologically altered leukocytes (toxic) have granules. The granules are basophilic and not neutrophilic. The expression neutrophil leukocytes is therefore out of order, and should be replaced by finely granulated leukocytes. Pathologic granules in acute infectious diseases are not developed to a maximum at first, but only after several days, as in lobar pneumonia during the crisis.

AUTHOR'S SUMMARY (in part)

THROMBOSIS AND EMBOLISM IN POST WAR YEARS T. K. KUHN, Mitt a d
Grenzgeb d Med u Chir **41** 329, 1929

In the postmortem examinations at Freiburg from 1921 to 1925, there was an increase in thrombosis from 11.3 to 24.5 per cent and an increase in fatal embolism from 1.3 to 4.9 per cent. The report concerns 665 cases of thrombosis and 105 of fatal embolism encountered in the years 1919 to 1927. After elaborate statistical evidence is offered, the author concludes that thrombosis affects most people between the ages of 41 and 50 years and fatal emboli are seen mostly between the ages of 51 and 60 years, that thrombosis and embolism are more common in men than in women, that cardiac dilatation and hypertrophy precede thrombosis and embolism more frequently than any other disease, that thrombi and emboli are met with most frequently in the internal medical clinics, 31.6 per cent in 1927 as against 24.3 per cent in surgical clinics and 25 per cent in gynecologic clinics. The increase in the medical clinics is traceable directly or indirectly to the increase in intravenous therapy. Infections were associated with local thrombosis only in the first year after the war. Obesity is regarded as predisposing to embolism because 50 per cent of obese people died of emboli in the lungs whereas only 2.2 per cent of cachectic people were found dead from this cause.

GEORGE RUKSTINAT

TOTAL ALYMPHOCYTOSIS L. R. GROTE and B. FISCHER-WASELS, Munchen med
Wchnschr **76** 2040, 1929

The authors report the case of a man, aged 39, with attacks simulating pancreatitis and indefinite symptoms of stenosis of the small bowel. After an illness of several months the increasing cachexia became associated with ascites and edema that were neither cardiac nor renal. The blood changed from normal to a complete absence of lymphocytes. Postmortem examination disclosed a total atrophy of the lymphatic system and of the spleen.

EDWIN F. HIRSCH

A MALIGNANT THYOMA WITH METASTASIS TO THE CENTRAL NERVOUS SYSTEM IN A CHILD THREE AND A HALF YEARS OLD F. DANISCH and E. NEDELMANN, Virchows Arch f Path Anat **268** 492, 1928

The author discusses a malignant lymphocytoma of the thymus with metastases to the central nervous system, cervical lymph nodes, heart and kidneys. An interesting aspect of the case is a marked pleocytosis of the spinal fluid due to the presence of numerous tumor cells.

K. Hosoi

THE CHANGES IN LIVER WOUNDS AFTER PACKING WITH FREE AND ATTACHED OMENTAL GRAFTS OSKAR LEWIN, Virchows Arch f path Anat **272** 31, 1929

In sixteen rabbits a liver wound was packed with a free omental graft, and in sixteen others with a pedunculated graft. The animals were killed and examined at various times thereafter. The changes in the liver tissue were the same in

both series. The "pluripotent Kupffer cells" play the most important role, they form histiocytes, macrophages, fibroblasts, new capillaries and myeloid blood cells. No regeneration of liver cells was seen but some overgrowth of young bile ducts. The attached omental graft can be transformed into connective tissue within ten or twelve days, with the free graft it takes at least fourteen days, occasionally forty-one days. Large parts of the free grafts become necrotic. The amount of necrosis depends on the extent of necrosis in the edges of the wound in the liver.

ALFRED PLAUT

ACQUIRED NODULAR SYPHILIS OF THE LUNG. FRANZ WINDHOIZ, Virchows Arch f path Anat **272** 76, 1929

One of the few really convincing cases of syphilis of the lung is reported. The patient was 73 years old and died suddenly from extensive aortitis syphilitica and arteriosclerosis. There were no tuberculous lesions. The gummas were situated in the middle lobe of the right lung only. The diagnosis was made from the gross specimen. The collagenous and elastic fibers were well preserved in the necrosis and the granulation tissue. The Wassermann test and the Meinicke reaction were strongly positive.

ALFRED PLAUT

THE CAUSE OF ACCIDENTAL INVOLUTION OF THYMUS GLAND. A. BABES, Virchows Arch f path Anat **272** 93, 1929

The accidental involution of the thymus (Hammar) is no simple atrophy. The sclerosis and the storing of different fat substances and of iron speak against it. It is not due to general nutritional disturbances, but to inflammatory processes in the lung. The older the inflammatory disease of the lung, the more marked is the accidental involution of the thymus. Among forty-four cases, only one showed accidental involution without an inflammatory process in the lung. Babes believes that toxic substances originating in the inflamed lung cause the accidental involution of thymus.

ALFRED PLAUT

THE IMPORTANCE OF THE RETICULIN FIBERS IN TUBERCULOSIS. P. A. ELIASCHEWITSCH, Virchows Arch f path Anat **272** 151, 1929

The noncellular tissue constituents often are neglected. Even the youngest and smallest tubercles, which do not yet contain giant cells, have a reticulum. There are a few fine fibers in the center, and there is a peripheral fibrillary layer. Small resorption tubercles in the surroundings of cheesy areas are best suited for the study. The reticulum is present before any healing tendencies, any fibrous change or any attempts at separation from the surroundings can be noted. The reticulum fibers ("Gitterfasern") are highly resistant to caseation. The fibrous change in a tubercle often is due to thickening of the existing reticulum rather than to multiplication of fibroblasts. With the growth of the tubercle, the fibers hypertrophy and finally become collagenous. The concentric, often entirely enclosed, fibrillary system of the tubercle seems to be important for the fixation of bacilli and toxins. In fact, bacilli can be found directly on the fibrils or the lamellae between them. The reticulum seems to have some adsorptive immunologic action. One must not think of the reticulin fibers as a merely mechanical device. The physicochemical condition of the reticulum may well play a role in the localization of the tuberculous process.

ALFRED PLAUT

TISSUE CULTURE OF HUMAN CHORIONIC EPITHELIUM. E. A. H. FRIEDHEIM, Virchows Arch f path Anat **272** 217, 1929

The question whether the large cells that are found deep in the muscle of the puerperal uterus are chorionic cells that have migrated or are formed from the

mesenchyma cannot be answered by usual histologic methods. Therefore tissue cultures were made from chorionic villi of a 5 weeks old tubal gestation. The result favors the theory that these cells are migrating Langhans cells because the cells grow very well and in pure epithelial culture from the beginning. They liquefy the medium moderately and are motile. The syncytial cells, on the other hand, do not liquefy the medium and they do not grow at all. Isolated fragments of syncytial protoplasm, however, containing no nuclei, may show motility for several hours.

ALFRED PLAUT

COMPLICATED MALFORMATION OF UROGENITAL ORGANS F. A. LENTZE,
Virchows Arch f path Anat **272** 279, 1929

Ball-shaped dilatation of the ureter above the bladder is reported, with cystic horse-shoe kidney, double ureter on the other side, diverticulum of the bladder, dilatation of the urethra, malformation of the sphincter, marked hypoplasia of the prostate, absence of both seminal vesicles and of one vas deferens, large utriculus, scoliosis, spina bifida and clubfeet.

ALFRED PLAUT

THE OS SACRUM E. BRACK, Virchows Arch f path **272** 295, 1929

There is reported the absence of a sacrum in a new-born infant with extremely hypoplastic lower extremities, fracture of the os sacrum causing periproctal hemorrhage, ruptured sacral meningocele causing death through loss of cerebrospinal fluid in a 61 year old woman, smaller similar unruptured cyst in a man 80 years old.

The cartilaginous nodules may occur in the disks of the os sacrum.

ALFRED PLAUT

GAUCHER-LIKE CHANGES IN THE SPLEEN OF TAR-PAINTED RABBITS A. BABES,
Virchows Arch f path Anat **272** 411, 1929

Three of five rabbits which died between the tenth and twentieth day after the onset of tar painting had Gaucher-like changes in the spleen. The spleen is large, chocolate brown, with few and small follicles. The slides can hardly be recognized as spleen since most of the tissue is supplanted by strands and alveoli of large clear Gaucher-like cells, mostly from 18 to 30 microns in diameter, with large clear central nucleus and one or two nucleoli. The protoplasm contains no lipid substance, little iron is stored. Most of the large cells are situated within a sinus, few within a pulp cord. In this respect the condition differs from Gaucher's disease of spleen. L. Pick has seen the slides and agrees that the cells are similar to those found in Gaucher's disease. It is important to have a Gaucher-like condition which is caused by a well defined substance.

ALFRED PLAUT

AMYLOID DEPOSITS IN SEMINAL VESICLES ELMAR ERLACH, Virchows Arch f
path Anat **272** 418, 1929

A description of three cases is given. The condition is rare. Since its gross appearance is not unlike that of tuberculosis with caseation, some cases may be overlooked at autopsy.

ALFRED PLAUT

PERIARTERITIS NODOSA JOSEF BALO and E. NACTNEBEL, Virchows Arch f
path Anat **272** 478, 1929

Nine cases were observed in Budapest within three years. The disease seems to be more frequent in Germany and Austria than in other countries. The authors think that the disease is infectious. Many cases have been observed.

among stags in a park in the south of Germany. All nine cases were diagnosed from the gross aspect at autopsy. In five patients who had no nervous symptoms, severe lesions were found in the blood vessels of the nerves, but no marked degeneration of the nerve substance. Thus the nerve degeneration cannot be caused by the vascular lesion alone. Animal inoculation failed.

ALFRED PLAUT

SPLENOMYCOSIS AND MYCOTIC SPLENO-MEGALY. A. A. ABRIKOSOFF, *Virchows Arch f path Anat* **272** 593, 1929

Abrikosoff retracts his statement of 1928. He now believes that the formations in the spleen which have been described by many authors, especially the French, have nothing to do with mycelium. He believes that they originate (as German authors and some of the French always believed) from incrustation of connective tissue fibers, fibrin or erythrocytes. The round bodies that have been described as fructification organs of the fungus are too variable in size, and similar structures can result from iron salt solutions *in vitro*. The fact that *Aspergillus* may be grown from such spleens does not prove that the incrustations in question are mycelium. Thus no mycotic splenomegaly has been proved and the existence of such a disease is not probable.

ALFRED PLAUT

MARKED FUNNEL CHEST. FRANZ STADTMÜLLER, *Virchows Arch f path Anat* **272** 641, 1929

The author gives an exact description of a funnel-breast. In spite of the malformation, the heart was nearly in normal position. There was a large vertical space-furrow in the right lobe of the liver without a fold of diaphragm in it. This confirms Westenhofer's conception that these folds are due to lateral compression of the liver.

ALFRED PLAUT

ECHINOCOCCUS DISEASE OF THE PELVIC BONES. FRANZ AITMANN, *Virchows Arch f path Anat* **272** 662, 1929

From 1 to 2 per cent of *Echinococcus* infections are located in the bones. Next to the spine, the pelvis is the preferred site. In the pelvis the disease generally starts in the region of the acetabulum.

A woman, aged 46, had had symptoms in the right hip for twenty-six years. She fell down several times. Eighteen years before the present observations she was operated on for *Echinococcus* in the abdomen. She died shortly after two operations which were necessitated by excessive swelling of the hip region and thigh. The pelvis, both thighs and the corresponding muscle were removed from the body at autopsy. Large cysts were found in the muscles of the thigh and the pelvis. Most of the upper end of the femur was destroyed. There was severe destruction of all pelvic bones on the right side. Bone sequestrs contained numerous small vesicles. The bone was destroyed by lacunar arrosion with formation of sequestrs. The bone marrow contained granulation tissue with giant cells, there were no thick connective tissue capsules around the parasites. Many small, partly calcified osteoid layers were present. Some isolated, lime-free spots (Pommer's method) in otherwise normal spongiosa were suggestive of halisteresis.

Similar lesions were found in the museum specimen from an autopsy by Rokitsky in 1834. The tissue could be cut and stained well.

Fifty-three cases of primary *Echinococcus* disease of the pelvis are enumerated in a classified list.

ALFRED PLAUT

THE REGRESSION OF EXPERIMENTAL LIPOIDOSIS IN THE RABBIT EYE. A. A. KOLEN, *Virchows Arch f path Anat* **272**.679, 1929

Experimental lipoidosis in the rabbit eye is similar to gerontoxon in man. There is a difference in that the lipid material in gerontoxon is mostly situated

in connective tissue structures, and not in cells. After cessation of the cholesterol feeding, very strong experimental lipoidosis may remain up to three years. During the regression, the crescent-shaped lipoidosis occasionally shifts toward the center of the cornea. The periphery partly becomes clear. During regression, the infiltrated parts of the cornea become mottled and glistening like mother-of-pearl. Similar regressive changes are noted occasionally in gerontoxon in man. In the rabbit the superficial vascular layer of connective tissue forms during regression of very marked lipoidosis.

ALFRED PLAUT

SOCALLED EXPERIMENTAL CHOLESTERIN STEATOSIS OF RABBIT AND OTHER ANIMALS. S. S. CHALATOW, *Virchows Arch f path Anat* **272** 691, 1929

Cholesterin steatosis is complex. In any experiment one should take account of qualitative and quantitative variations carefully. The irritation that anisotropic lipoids exert on cells is due to their physical nature, it is not chemical. Tumorous xanthomas are formed by the same process. Chalатов denies the existence of a physiologic reticulo-endothelial system. The fact that the Kupffer cells, for instance, retain corpuscles and micro-organisms has nothing to do with phagocytosis. Anisotropic fatty change is always preceded by infiltration with isotropic fat. The cholesterin steatosis has different localization in different animals (intima of the aorta in man). Sclerosis and xanthomatosis exclude each other, as one can see in syphilitic aortitis. While interpreting the results of feeding experiments on goats, the author again stresses the complexity of the problem and hints that not all the conclusions drawn in the literature are valid.

ALFRED PLAUT

THE FROG'S TONGUE AFTER THE INJECTION OF INDIA INK INTO THE BLOODSTREAM. W. SCHOPPER, *Virchows Arch f path Anat* **272** 709, 1929

The storage of india ink is a purely physical process. The cells of the walls of peripheral blood vessels also can store the india ink, as can be seen on the tongue of the living frog. They do not store as intensely as do the reticulum cells of the spleen and the Kupffer cells in the liver. In the experiments, the tongue was gently stretched over a ring of cork, the animal was anesthetized by the injection of urethane into the dorsal lymph sac. Lymphocytes and large monocytes stored the india ink also, neutrophil and eosinophil leukocytes remained nearly free. The india ink was located on granulations in the cells of the vessel wall. Most of the monocytes probably originated from the lining cells of liver capillaries. In the course of weeks, the india ink was brought into the perivascular tissue by means of the adventitial cells.

ALFRED PLAUT

THE REACTION OF THE ENDOTHELIUM OF THE RABBIT CAROTID ARTERY AFTER DOUBLE LIGATION. B. F. MALYSCHFW, *Virchows Arch f path Anat* **272** 727, 1929

In the rabbit carotid, the endothelium rests directly on the inner elastic layer. There is no connective tissue between both. The vasa vasorum reach only into the outer muscular layers. Thus one can be sure that all cells found within the lumen of the ligated vessel originate from endothelium.

The experiments were done on forty-nine rabbits. The ligatures were made from 0.25 to 1 cm apart, sometimes the peripheral ligature was made first, and sometimes the central. The observations were made after different periods of time—from six hours to one year. In another group of animals the artery was cut between two double ligatures. The same was done in a third group, and the artery was then put into the peritoneal cavity of the rabbit. In some animals trypan blue was injected into the ear vein.

Practically no thrombosis took place. There was intensive overgrowth of the endothelial cells, not only parallel to the vessel wall but also at right angles, with the formation of so-called cavernoma. The endothelial cells became partly

separated from the vessel wall and grew like a tissue culture in the plasma of the blood. The red blood cells disappeared after four or five weeks only, when granulation tissue began to grow into the lumen. The leukocytes disappeared earlier, the lymphocytes being more resistant than the granular forms. There was no sign of multiplication of blood cells or of transformation into other forms. Between the first and the fourth week, complete hematopoiesis was observed in the doubly ligated part of the artery. The whole process was intravascular. The endothelial cells formed a connective tissue layer inside the internal elastic lamella, and in later stages this layer was transformed into a musculo-elastic layer. It is probable that these elastic fibers and muscle cells developed from the fibroblasts, which in turn originated from the endothelium. In the sections of artery which were put into the abdominal cavity, the tissue reactions were the same.

ALFRED PLAUT

EXPERIMENTAL INVESTIGATIONS ON SPLEEN CHANGES IN PERITONITIS. P. GOHRBANDT, *Virehows Arch f path Anat* **272** 763, 1929

It was the author's purpose to study changes in the spleen in peritonitis which have never been described in full in the literature. Dogs were laparotomized and a small piece from the spleen was excised. Then peritonitis was caused by opening the stomach, the colon or the gallbladder, or by bringing bacteria into the peritoneal cavity. Occasionally another biopsy was taken later. The dogs were killed by the injection of chloroform into the heart.

The dog spleen contains many more muscle fibers than that of the human being. There is a distinct perifollicular zone around the malpighian bodies; its cells are similar to those of the germ centers. Eosinophil cells are few. Polymorphonuclear leukocytes are always found, especially in the perifollicular zone under the capsule and along the trabeculae. There are plasma cells in the spleens of most dogs.

Swelling of the spleen was not found in any of the experiments. On the other hand, a bitch that had general septicemia after necrotic metritis showed swelling of the spleen at the time of death. The softness and swelling of the spleen as found in autopsies of human beings after septic diseases probably are mostly postmortem. Microscopic changes were present in every spleen examined. In order to appreciate these changes, it is necessary to have the comparison with the biopsy which was taken before the onset of the peritonitis. The malpighian bodies generally are not swollen and the germ centers not enlarged. Necroses are found frequently in the centers, occasionally in the perifollicular zone also. Very little necrosis was found in the pulpa. These lesions are similar to the ones described in infectious diseases and poisonings. The lymphoblasts are most damaged. The necrotic lesions were found more frequently after biliary peritonitis, they are probably toxic in origin.

The amount of histochemically demonstrable fat was increased, but the fat in the capillary sheaths shown by the biopsy was absent in the autopsy material. The necrotic spots were surrounded by much fat. The iron pigment was generally increased. The distribution of leukocytes was studied with the oxydase reaction. They increase in the first ten hours of peritonitis, they then decrease and appear mostly in the perifollicular zone. The true and the lymphoblastic plasma cells were generally increased in number. Myeloid metaplasia was found twice. The productive changes were mostly localized around the necrotic spots. There were some giant cells.

Even the most virulent cultures of *Bacterium coli* did not cause fatal peritonitis, not even when gauze was left in the peritoneal cavity and opiates were used to lower the intestinal activity. *Staphylococcus* cultures were not very efficient either, while streptococci proved more virulent.

ALFRED PLAUT

TRAUMATIC ANEURYSM HAROLD BORCHARDT, Virchows Arch f path Anat
273 163, 1929

A man aged 19 years, fell while walking. He hit a stone with his left side and broke a rib. For the next thirty years he continuously had pain in the left side. Forty-five years later, while he was in bed in a hospital (with jaundice), he suddenly died with the symptoms of internal hemorrhage. A circumscribed shadow in the left side of the chest had been seen in the x-ray picture. Autopsy revealed an aneurysm of the muscular branch of the left fourth intercostal artery. It had eroded the bone of the rib and of the vertebra considerably. Thus the pain which the man had had for thirty years is explained by the pressure of the nerve root.

ALFRED PLAUT

THE TAR AND CHOCOLATE CYSTS OF THE OVARY F ISBRUCH, Ztschr f
Geburtsh u Gynak 94 710, 1929

In a woman with complete obstruction of the cervix, tar cysts were found in both ovaries. Dysmenorrhea was present for many years, but no hemorrhage. The case is not considered as a proof of Sampson's implantation theory of the origin of endometrial cysts due to retrograde menstruation, as there is still definite evidence lacking that endometrial tissue desquamated during menstruation is able to become implanted and to grow successfully. This question may be decided through tissue cultures of endometrial tissue.

W C HUEPER

DIFFUSE MELANOSARCOMATOSIS OF THE SOFT MENINGES J KRAFT, Ztschr f
Krebsforsch 29 74 1929

A case is reported of primary diffuse melanotic tumor of the soft meninges of the brain and cord. Although its microscopic appearance was that of a sarcoma, there was nowhere evidence of metastasis outside of the leptomeninges, but here the tumor appeared to be capable of indefinite extension, even into the clefts and sulci of the brain and cord surfaces. The writer cites a small number of similar cases previously reported.

H E EGGERS

PECULIAR PROPERTIES OF CANCEROUS PLEURAL EXUDATE H AULER and P
MEYER, Ztschr f Krebsforsch 30 286, 1929

In the pleural exudate formed as a result of metastasis of a cancer of the breast, the writers have found a high content of complement, the more remarkable because cancerous serum ordinarily shows a great reduction in this component. Unlike the normal complement of guinea-pig serum, this withstood from twelve to fourteen days' storage in the icebox. Another peculiarity lay in the fact that after separation of the rapidly developing spontaneous clot, there was further clotting on the addition of alcoholic antigens diluted as for the Wassermann test.

H E EGGERS

THE EXPLANTATION OF ENDOMETRIUM P CAFFIER Zentralbl f Gynak 52 63,
1928

A veil-like membrane always developed around the explanted endometrium, regardless of during which phase of the cycle the endometrial tissue was explanted. Decidua of the first months showed the same product. A separation of the cells in the cellular sprouts around the explanted tissue into cells of different origin was not possible. Endometrial tissue desquamated during menstruation could not be successfully cultured. Definite conclusions from these results could not be drawn on Sampson's theory of endometriomas.

W C HUEPER

INFILTRATIONS IN SMALL INTESTINE WITH PLASMA CELLS U QUENSEL, Finska lak-sällsk handl 71 661, 1929

In a man, aged 44, with a history of long-continued gastric disturbance and treatment for duodenal ulcer, there occurred suddenly great exhaustion with bloody feces and death in a week. Necropsy revealed numerous firm, round and oval foci of various sizes. Most of the mucous membrane was intact. Microscopic examination showed a diffuse infiltration of the intestinal wall with round cells, chiefly plasma cells. In and among these cells were peculiar, sharply defined foreign corpuscles of irregular form and size. It is suggested that the process may perhaps be regarded as a new mycotic disorder of the intestine.

Pathologic Chemistry and Physics

SOME PHYSIOLOGICAL ASPECTS OF COPPER IN THE ORGANISM F B FLINN and J M INOUE, J Biol Chem 84 101, 1929

Ingested copper is eliminated, almost entirely, in the feces. A part becomes intermediately absorbed into the body but is rapidly returned to the intestines in the biliary excretions. The distribution of copper in the tissues of the rat, and in the livers of the different animal species, the affinity of the metal for protein, and especially for mucin, and the possibility that copper may favor growth and hemoglobin production are discussed.

ARTHUR LOCKE

THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN ECLAMPSIA H J STANDER, N J EASTMAN, E P H HARRISON, JR, and J F CADDEN, J Biol Chem 85 233, 1929

Severe eclampsia is associated with a true acidosis, due to an uncompensated alkali deficit. The organic acid content of the blood is increased, and the pH is decidedly lowered. There is no increase in organic acid content or any abnormal reduction in the pH of the blood during normal pregnancy.

ARTHUR LOCKE

THE NATURE OF THE EFFECT OF A HIGH-FREQUENCY ELECTRIC FIELD UPON PARAMÆCIUM H KAHLER, H W CHAIRLEY and CARL VOEGTLIN, Pub Health Rep 44 339, 1929

It is shown that the only demonstrable effect of the exposure of *Paramæcium caudatum* to a high-frequency electrostatic or electromagnetic field is that primarily caused by a temperature increase in the organism. This conclusion is in agreement with deductions made from physical considerations of the effect of the high-frequency field on nonliving systems. Valid conclusions can be obtained only if due consideration is given to the control of certain complicating factors, such as the so-called skin effect and the energy output of the generating circuit.

AUTHORS SUMMARY

CRITICAL TEMPERATURE OF FREEZING LIVING MUSCLE J MORAN, Proc Roy Soc s B 105 177, 1929

In the removal of water from living amphibian muscle, either by freezing or drying, three zones may be distinguished. (1) up to 40 per cent, over which the original state of muscle is completely recovered by restoring water. (2) between 40 and 78 per cent, in which the physiologic activity of the muscle progressively diminishes but its physicochemical properties are unaltered, (3) beyond 78 per cent, in which the muscle immediately dies. The critical water removal of 78 per cent corresponds to the freezing of the muscle to equilibrium at about -2°C .

Muscles frozen to equilibrium below -2°C undergo marked changes on thawing, such as (1) shortening up to 80 per cent of the length of the muscle, (2) expression of a strongly acid fluid, (3) total loss of irritability and (4) complete loss of osmotic properties. Of these the shortening alone can be prevented, it does not occur when the frozen muscle is very slowly thawed. Muscles supercooled below -2°C (e.g., for two days at -4°C) do not undergo irreversible change. They appear to be normal when restored to room temperature.

AUTHOR'S SUMMARY

THE FORMATION OF LACTIC ACID IN THE MUSCLES IN THE FROZEN STATE. E. C. SMITH, *Proc Roy Soc s B* **105** 198, 1929

A normal muscle with an adequate supply of oxygen is in a steady state in which the rate of production of lactic acid and of its removal are so balanced that the percentage of acid at any moment remains at a very low constant level. Freezing, that is, drying, upsets this balance by making the rate of production exceed that of removal. The upset in the balance is due to, or is accompanied by, injury to the mechanism, but in a storage period of twenty-four hours at temperatures between the freezing point and -16°C , the mechanism of removal is not destroyed so that on thawing the accumulated acid is removed completely. Below -16°C the mechanism of removal of acid is destroyed while that of production persists. Is it fair to ask whether the mechanism of removal is not the "living" part?

AUTHOR'S SUMMARY

THE CHEMICAL BASIS AND THE CLINICAL SIGNIFICANCE OF PROTEIN DIFFERENTIATION IN THE SERUM. ANTON FISCHER, *Klin Wchnschr* **8** 2328, 1929

Tryptophan estimations, which are an indirect chemical method for determining the albumin-globulin ratio, have a greater significance as a clinical indicator for active inflammatory diseases than the sedimentation reaction, especially in rheumatic diseases.

The diminution of the cystine content of pathologic serums is further evidence that under conditions that result in a globulin increase of the serum there are profound chemical changes of the serum proteins.

According to the results obtained, the globulin fraction is a mixture of four, and the albumin of three, chemically different proteins.

AUTHOR'S SUMMARY

Microbiology and Parasitology

SPONTANEOUS BACILLURIA AND PYELITIS IN THE RABBIT. HENRY F. HELMHOLZ, *Am J Dis Child* **38** 968, 1929

Bacilluria is an infrequent observation in the catheterization of rabbits as a routine and is usually due to a gram-negative bacillus. The bacilluria is usually limited to the bladder but occasionally involves also the pelvis and the kidney. Exceptionally, cystitis, pyelitis and pyelonephritis are found in the rabbit. The frequency of bacilluria limited to the bladder and the relative infrequency of infection of the upper urinary passages make it probable that the exceptional bacilluria of the upper urinary tract and pyelonephritis are the result of an ascending infection from the bladder. So far as this study of spontaneous urinary infection is applicable to conditions in human beings, the conclusion seems warranted that infections of the urinary tract in infants take place by the ascending route.

AUTHOR'S SUMMARY

MULTIPLE DISSEMINATED LUPUS VULGARIS [EMBOLIC TUBERCULOSIS] VAUGHN
C GARNER, Am J Dis Child **38** 1028, 1929

The disease is due to tubercle bacilli which reach the skin as emboli from an underlying focus which is usually glandular. In the majority of cases an exanthem, most often measles, acts as the exciting cause of this tuberculous dissemination. Clinically, the skin lesions are papular or verrucose, widespread and indurated. The association of tuberculous bone lesions is not infrequent. The ultimate prognosis must be guarded, an eventual mortality of 20 per cent is to be expected. The pediatrician's interest in this supposedly rare entity is solicited, a knowledge of its clinical features should lead to more frequent recognition.

AUTHOR'S SUMMARY

UNDULANT FEVER PRESENTING THE CLINICAL SYNDROME OF INTERMITTENT
HYDRARTHROSIS B M BAKER, JR, Arch Int Med **44** 128, 1929

A case of infection by *Bacillus abortus* arising in Virginia is reported. In addition to many of the features of undulant fever, the patient presented a periodic swelling of the knee joints, diagnosed intermittent hydrarthrosis. Organisms of the *Brucella melitensis* group were isolated repeatedly from the blood stream and from fluid from the knee joints. Specific agglutinins appeared in the blood after the administration of an autogenous vaccine. Definite disappearance of the signs and symptoms of the infectious disease followed the administration of *Brucella melitensis* vaccine and serum from a patient who had recovered from undulant fever. There was amelioration of the subjective joint disturbances and a temporary alteration in the hydrarthrosis following this treatment. It is concluded that in this case the intermittent hydrarthrosis was part of the general picture of infection from *Brucella melitensis*, and it is suggested that infection by a member of this group of organisms might prove to be the cause of the clinical syndrome, intermittent hydrarthrosis, in other patients.

AUTHOR'S SUMMARY

MENINGO-ENCEPHALITIS DUE TO TORULA W J STONE and B F STURDIVANT,
Arch Int Med **44** 560, 1929

There was a focus of torulosis in the apex of the right lung which is regarded as primary. The lesions of torulosis have numerous giant cells containing torulae but are free from polymorphonuclear leukocytes. All cases so far reported of *Torula meningitis* have ended in death.

THE RELATIONSHIP OF THE FLAVOBACTERIUM OPHTHALMIAE TO PERIODIC OPHTHALMIA IN HORSES ALAN C WOODS and E L BURKY, Arch Ophth
2 456, 1929

Investigations were made with a view to determining whether the asserted etiologic relationship of Rosenow's *Flavobacterium ophthalmiae* to moon blindness of horses could be confirmed. The organism as supplied by Rosenow was proteolytic and nonacid-forming. Cultures were taken, according to Rosenow's technic, from horses in which the disease was active as well as from normal horses. Fodder and farm water were also cultured. Cultures from normal and those from affected animals kept under the same conditions were both positive in about the same percentage, cultures from horses on farms on which the disease did not exist were positive a little less frequently than cultures from affected animals. On farms on which the disease was present, the organism was found in one of three cultures made of the fodder. No cultures of fodder from unaffected farms were made. No conclusions could be drawn from the results of cultures from the water supply. Four animals with acute exacerbation were killed, the eyes removed and cultures made under various conditions and on various mediums. These were all negative. The same results were obtained with the eyes of horses

in which the disease was quiescent. Agglutination tests showed apparently no difference in the agglutinative powers of serums from normal and affected horses toward this organism and no difference in the agglutinative power of an immune serum toward strains isolated from affected and normal horses. Intravenous injection of this organism did not affect the eyes. Intra-ocular injection produced moderate secondary uveitis, not comparable with periodic ophthalmia from either the clinical or the pathologic standpoint. Similar tests were made with broth cultures and filtrates of *B. prodigiosus* and *B. pyocyaneus* on rabbits, as well as with *Flavobacterium ophthalmiae*, and the results were found exactly similar in all three, a reaction that seems to be due to a product of protein degeneration. The authors conclude that *Flavobacterium ophthalmiae* is not the etiologic agent of periodic ophthalmia.

CHARLES WEISS

FILTRABLE AGENT IN PERIODIC OPHTHALMIA OF HORSES. ALAN C. WOODS and A. M. CHRSNEY, Thirteenth Concilium Ophthalmologicum, Amsterdam, Dan Haag, September, 1929.

A filtrable agent has been isolated from the eyes of horses affected with periodic ophthalmia. This agent has been passed through successive generations of rabbits by intra-ocular injections, producing the picture of an exudative retinitis. After passage through rabbits, it has again been transmitted to horses by intra-ocular injections, producing the pathologic picture found in the spontaneous disease.

THE EFFECT UPON HAEMOLYTIC STREPTOCOCCI OF CULTIVATING THEM IN IMMUNE AND NORMAL SERUM. ELEANOR A. BISS and HAROLD L. AMOSS, Bull. Johns Hopkins Hosp. 45:361, 1929.

Two strains of erysipelas streptococci were found, after cultivation in homologous immune serum, to have deteriorated in toxigenicity and in pathogenicity for rabbits, while the same strains cultivated in normal horse serum maintained their original potency. In broth, the normal serum strain as well as the original culture produced a coarse precipitate, while the immune serum strain grew diffusely. The other biologic properties, such as fermentation reactions, hemolytic power and colony formation, of the two strains remained unchanged. Two kinds of colonies, rough and smooth, were observed on plates from the immune serum series and the original cultures. There was no difference in the pathogenicity for rabbits of a rough and smooth colony strain from a given culture. Those from the normal serum were equally virulent, while those from the immune serum were equally attenuated.

AUTHORS' SUMMARY

UNDULANT FEVER. W. M. SIMPSON and E. FRAIZER, J. A. M. A. 93:1958, 1929.

Sixty-three cases of undulant fever have been discovered in and about Dayton, Ohio, during the past year. The rapidly increasing number of reported cases in the United States indicates the seriousness of this disease as a public health problem. Contrary to previously expressed beliefs as to the difficulties encountered in making a clinical diagnosis of undulant fever, the clinical picture of the disease was sufficiently characteristic to enable several physicians to make an initial diagnosis of undulant fever in more than one third of our cases. There appears to be no etiologic factor other than the ingestion of raw milk and unpasteurized dairy products in the cases studied. No cases of direct porcine or caprine origin were encountered. *Brucella abortus* was recovered from the blood of five patients suffering acutely from the disease. The organisms were found to be serologically identical with the strains recovered from the milk of five cows supplying raw milk to these patients. The blood was found to agglutinate *B. abortus* and *B. melitensis* in high titers. All were raw milk consumers. In three human cases of suppurating seminal vesiculitis, prostatitis, epididymitis and orchitis, antiabortus agglutinins were present in high titer. The organism was recovered from a

drawing sinus tract of the scrotum in one case. The intradermal test utilizing a suspension of killed *abortus* organisms seems to hold considerable promise as an adjunct to the agglutination test.

AUTHORS' SUMMARY

THE SPECIFICITY OF SCARLATINAL HEMOLYTIC STREPTOCOCCI. GLORIA MORIWAKI, *J. Bact.* 18: 139, 1929.

In no respect has an absolute specificity of scarlatinal hemolytic streptococci been established. Every biologic as well as antigenic property tested seems common to a certain extent among strains of hemolytic streptococci from various sources. Especially, it is worth while to note that the rash-developing property is not limited to scarlatinal strains. These facts superficially seem to show that hemolytic streptococci primarily have no relation to the etiology of scarlatina, as was believed by Jochmann and others. But on the other hand, the fact that filtrates of broth culture of scarlatinal hemolytic streptococci contain scarlatinal antigen is well established, as shown by their rash-developing property and Schultz-Charlton's blanching phenomenon. Hemolytic streptococci from other sources also produce such an antigen. Therefore, the presence of a special filtrable virus of scarlatina may be doubted simply because the presence of such special virus, if any, together with streptococci from other sources than scarlatina is difficult to understand. The rash-developing power and the property of evoking Schultz-Charlton's phenomenon are properties of scarlatinal hemolytic streptococci, but these properties are common to hemolytic streptococci from other sources though in quantitatively less degree. Is there an unknown virus which makes hemolytic streptococci active? This is another problem. Finally the question arises as to the nature of scarlatinal symptoms. Are they toxic or allergic in relation to the product of the scarlatinal strain? The question has to be decided by further experimental studies.

AUTHORS' SUMMARY

BACTERIOLOGY OF THE BLOOD AND JOINTS IN RHEUMATIC FEVER. RUSSIE L. CECIL, EDITH E. NICHOLS and WILFRED J. STAINSBY, *J. Exper. Med.* 50: 617, 1929.

During the spring of 1928, twenty-nine patients with acute rheumatic fever were subjected to blood cultures, of whom nine, or 31 per cent, yielded a streptococcus. During the spring of 1929, thirty-one patients with acute rheumatic fever were studied by blood cultures, of whom twenty-six, or 83.9 per cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods. Of the thirty-five strains of streptococci recovered from blood cultures, thirty-three have been classified as alpha streptococci (*Streptococcus viridans*), one as a beta streptococcus (*Streptococcus hemolyticus*), and one a gamma streptococcus (*Streptococcus anhemolyticus*). Some of the viridans strains produced very little green on blood mediums. Agglutination and absorption tests indicate that the strains of *Streptococcus viridans* recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biologic groups. In seven patients with rheumatic fever who were subjected to cultures from affected joints, five, or 71.4 per cent, yielded *Streptococcus viridans*. In three patients in whom green streptococci were recovered from both the blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources. These observations corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection, usually of the alpha or viridans type. The pathogenesis of rheumatic fever in respect to the joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent on localization of bacteria in the joint, with subsequent infection.

AUTHORS' SUMMARY

DEVELOPMENT IN TISSUE CULTURES OF THE INTRACELLULAR CHANGES CHARACTERISTIC OF VACCINAL AND HERPETIC INFECTIONS T M RIVERS, E HAAGEN and R S MUCKENFUSS, J Exper Med **50** 665, 1929

Characteristic vaccinal and herpetic lesions, including Guarnieri's bodies and acidophilic nuclear inclusions, respectively, regularly occur in rabbit corneas infected and cultivated in vitro according to the method here described

AUTHORS' SUMMARY

STAPHYLOCOCCAL INFECTION AND REINFECTION P N PANTON and F C O VALENTINE, Brit J Exper Path **10** 257, 1929

Experiments are reported which showed that repeated reinfection with *Staphylococcus aureus* produced a partial tissue immunity as demonstrated by the smaller skin reaction in response to a normal infective dose. In addition there was a partial or complete general immunity, evidenced by the appearance of agglutinins and increased resistance to a lethal dose. However, a very small dose which caused no symptoms in the control animals produced a definite reaction in those which were reinfected. It is believed that this increased sensitivity may result in further lesions in spite of the antibacterial substances produced.

J N PATTERSON

TYPHUS FEVER RESERVOIR IN MAN S RAMSINE, Arch Inst Pasteur de Tunis **18** 247, 1929

The author investigated a small isolated group of persons near Belgrade to whom typhus had been brought from a region where typhus was endemic. Positive Weil-Felix agglutination titers and the existence of the infective virus as tested by inoculation of guinea-pigs were clearly demonstrated in the blood of persons without clinical symptoms. In a succeeding paper, Charles Nicolle points out the importance of the proof of the existence of a latent reservoir for the virus in regions where the disease persists.

M S MARSHALL

EVOLUTION OF SPIROCHETES IN THE TICK PIERRE HATT, Arch Inst Pasteur de Tunis **18** 258, 1929

The evolution of several species of spirochetes of recurrent fever in the bodies of *Oimithodorus moubata* and other ticks was studied. A fragmentation of the organisms was observed, resulting in a small stage, possibly a point of departure for a new cycle.

M S MARSHALL

ATYPICAL PLASMODIA IN GRAVE CASES OF MALARIA GEORGES VILLAIN, Arch Inst Pasteur de Tunis **18** 352, 1929

Sketches of atypical forms of *Plasmodium falciparum* in the schizont stage are appended. The author concludes as follows: "From the medical point of view, I believe I may conclude (1) If all cases of grave malaria are far from presenting atypical plasmodia, the existence, on the other hand, of abnormal hematozoa in the peripheral circulation signified nearly always severe case. (2) Thus there is an obligation to sample the peripheral blood of all malarial patients, either proven or suspected, apyretic or febrile, treated with quinine or not. The examination of this blood would naturally be practiced with all necessary care and patience. (3) The existence of atypical forms of plasmodia makes mandatory, whatever the apparent clinical form of the attack, the re-enforcement of specific treatment."

THE BIOLOGIC ACTION OF ROENTGEN-RAYS IN TUBERCULOSIS G BRDICZKA, Beitr z Klin d Tuberk **72** 298 and 312, 1929

Thirty-one patients with pulmonary tuberculosis were treated with roentgen rays, and their blood pictures were determined at frequent intervals. Most

frequently, the patients reacted with a leukocytosis, but other types of reactions occurred in a considerable percentage of patients

Normal and allergic guinea-pigs received intracutaneous injections of tubercle bacilli. Some of the resulting lesions were irradiated, others served as controls. Treatment with x-rays seemed to make no difference in the reinjection foci. In the primarily infected animals the irradiated lesions formed larger abscesses than the controls

MAX PINNER

THE VIRULENCE OF BCG O. KIRCHNER and E. A. SCHNIDDER Beitr z Klin u Tuberk **72** 673, 1929

A strain of BCG was transplanted in direct sequence into the cornea of ten successive rabbits. No increase in virulence was observed during this experiment, which lasted thirteen months. The reinoculation was always done before the corneal focus became vascularized. Foci produced by 0.0001 mg developed more slowly but reached the same extent and healed much more slowly than foci produced by 0.001 mg.

MAX PINNER

VIRULENCE AND TYPE OF BACILLARY STRAINS FROM CHILDHOOD TUBERCULOSIS H. OPITZ and SHERIF, Beitr z Klin u Tuberk **72** 523, 1929

One bacillus of a virulent culture may produce generalized tuberculosis in guinea-pigs. According to the determinations on twenty-three strains the virulence of the bacilli does not play a decisive role in childhood tuberculosis. Two of the twenty-three strains belonged to the bovine type, one was derived from a tuberculous peritonitis and one from a meningitis. The latter was probably associated with a strain of the human type.

MAX PINNER

THE VIRULENCE OF TUBERCLE BACILLI IN PULMONARY TUBERCULOSIS W. ROLOFF and W. PAGEL, Beitr z Klin u Tuberk **72** 685, 1929

Thirty-three strains of tubercle bacilli of the human type were isolated from sputum from different forms of pulmonary tuberculosis. Their virulence was tested by intracutaneous inoculation into guinea-pigs. The size and the development of the cutaneous focus made it possible to differentiate bacilli of higher and lower virulence, the former showing more histiocytic infiltration, ulceration and tubercle formation, while the latter showed more abscess formation. A relation between the virulence of the bacilli and the clinical course of the disease from which they were isolated was not apparent.

MAX PINNER

IMMUNOLOGICAL STUDIES OF MONKEYS AFTER INOCULATIONS WITH BCG F. GERLACH and R. KRAUS Zentralbl f Bakteriol (Abt 1) **110** 179, 1929

The authors injected BCG into monkeys (*Macacus rhesus*) in amounts of from 30 to 50 mg with no serious consequences, and observed the development of an immunity against later tuberculous infection to both the human and the bovine type of tubercle bacilli. The control monkeys under the same conditions developed a typical progressive tuberculosis. On the basis of these experiments, the authors conclude not only that progressive tuberculous processes resulting from virulent and pathogenic tubercle bacilli can give rise to an immunity to infection, but also that attenuated tuberculogenic but nonpathogenic strains of tubercle bacilli can confer immunity against virulent strains of both the human and the bovine type of tubercle bacilli.

PAUL R. CANNON

THE NATURE OF THE TOXICITY OF MANNITE-FERMENTING DYSENTERY BACILLI A. DE ASSIS, Ztschr f Immunitätsforsch u exper Therap **58** 343, 1928

The toxicity of a recently isolated Hiss Y type strain was tested by the intravenous injection of mice with four preparations: (1) old bouillon culture filtrate,

(2) filtrate of culture autolyzed in distilled water, (3) killed dried bacilli obtained by centrifuging a distilled water suspension, (4) wash water toxin, the supernatant of a centrifuged suspension of the bacteria dried, redissolved and centrifuged to clear of all insoluble material. Preparations 1 and 2 were nontoxic, 3 and 4 were toxic. Prolonged immunization of horses with these antigens gave negative results for antitoxin production. The author concludes that the toxicity of Hiss Y dysentery bacilli is bound up with the protoplasm and is not due to a toxin.

ROY C. AVERY

Immunology

UNDULANT FEVER IN RELATION TO PREGNANCY AND ABORTION E. L. CORNELL
and C. R. DE YOUNG, *Am J Obst & Gynec* **18** 840, 1929

Of 1,015 samples of serum from pregnant women in Chicago, none gave a definitely positive agglutination of *B. abortus* or *B. melitensis*. Five gave weak agglutinations. Of twenty-three serums from women who had aborted, one gave a reaction at 1:80.

INFLAMMATION AND IMMUNITY EUGEN L. OPIE, *J Immunol* **17** 329, 1929

The observations that have been described help to explain the changes that occur when an animal sensitized by infection with a suitable micro-organism is reinfected with the same agent. An inflammatory reaction of unusual intensity occurs and this reaction brings to the site of infection plasma containing antibodies. The experiments cited show that the two factors promote fixation and destruction of bacteria. Anaphylactic inflammation to which an animal repeatedly injected with foreign protein becomes susceptible protects the body from the injurious agent. The paradox between increased susceptibility to injury and the resistance of immunity is only apparent. The local injury that occurs is brought about not so much by the foreign agent introduced into the tissues, which, it is true, is fixed at the site of entry, as by the coming together of this antigen with antibody which is a product of immunization. The hypersensitiveness of infection, illustrated by the tuberculin reaction, is manifested by an acute inflammatory reaction that has all of the essential characteristics of anaphylactic inflammation. It has not been possible to demonstrate its relation to any antibody that finds its way into the blood serum but the evidence available does not exclude this relationship. The hypersensitiveness of infection that is usually manifested by reaction to products of the micro-organism concerned occurs under natural conditions in the presence of living bacteria that have invaded the body. The evidence I have cited shows that the acute inflammatory reaction produced in the sensitive animal by bacterial products retards bacterial invasion somewhat ineffectively at first, not only by bringing antibodies to the site of attack but by fixing bacteria at the site of entry so that they cannot enter the blood stream. Both with anaphylactic inflammation and with the inflammatory reaction of infected animals, vital organs are protected at the expense of local injury.

AUTHOR'S SUMMARY

ISO-AGGLUTININS IN CATTLE RALPH B. LITTLE, *J Immunol* **17** 377, 391, 401 and 411, 1929

The examination of the blood from 209 cows and 31 bulls for hemagglutination is reported. The presence of iso-agglutinins in the blood of bovines is established. It is possible to identify three principal groups, however, the anomalous reactions shown by some serums suggest additional grouping. In certain bloods agglutinin as well as agglutinable substance is present in the blood of the same individual. The agglutinins are labile and disappear on standing at room or refrigerator temperature. So far the different blood types seem to bear no relation to the

various breeds of cattle. When group I serum is heated at 60 C for one hour, the agglutinative substance is generally inactivated. A temperature of 56 C for one hour is not sufficient to inactivate all serums completely. When group I serum is heated at 60 C, one component of agglutination is destroyed. With the addition of fresh unheated serum from certain cows, this component is again restored.

AUTHORS SUMMARY

THE DICK TEST AND ALLERGIC SKIN REACTIONS TO STREPTOCOCCUS NUCLEO-
PROTEINS K ANDO, J Immunol 17 361, 1929

From the Dick toxin two substances have been obtained with which skin reactions can be produced in human beings: a nucleoprotein and a specific toxin. The so-called nucleoprotein causes a skin reaction that cannot be distinguished from that caused by ordinary Dick toxin; it is heat-stable and nontoxic for man; it does not cause any skin reaction in white pigs. By repeated alcohol and acid precipitation a relatively pure specific toxin can be obtained from culture filtrates of *Streptococcus scarlatinae*; this causes reactions in the skin of human beings and white pigs; it is destroyed by heating to 80 C for thirty minutes, and its action is neutralized by scarlatinal antitoxin. Susceptible persons can be immunized with it. In the course of immunization the scarlatinoid syndrome was observed in some cases. No evidences of allergy could be obtained with the true toxin-exotoxin, but the nucleoprotein gave rise to an allergic condition and a skin reaction to the protein may be regarded as allergic. The nucleoprotein may influence the reaction to the ordinary Dick toxin, especially if it is weak in true toxin. High dilutions of potent toxin should be used preferably, and the Washington standard toxin was found to be very satisfactory as it contained traces only of nucleoprotein.

HORSE SERUM AS A HETEROPHILIC ANTIGEN I DAVIDSON and S G
RAMSDEIL, J Immunol 17 365, 1929

There are present in horse serum heterophilic antigens of the Forssman type, as shown by the development of a relatively strong antishoop hemolysin in rabbits immunized with large quantities of the serum. Absorption with heterophilic organs removed the hemolysin, while absorption with nonheterophilic organs diminished its titer only slightly, possibly due to physical absorption. The immune serums did not contain agglutinins for sheep red cells, neither did they contain hemolysins and agglutinins for horse and guinea-pig red cells. Antistreptococcus serum has antigenic qualities similar to those of plain horse serum, while diphtheria globulin does not stimulate the production of heterophilic antibodies, and subcutaneous injection of any one of the three serums fails to call forth a response. The serums of rabbits, as a result of the treatment outlined, become toxic for the guinea-pig. This toxicity is shown to be not identical with the sheep cell hemolysin.

AUTHORS SUMMARY

HYPERSENSITIVENESS TO DIPHTHERIA BACILLI JAMES M NEILL and WILLIAM
L FLEMING, J Immunol 17 419, 1929

The present example of diphtheria bacterial hypersensitiveness agrees with the previous examples in that it is manifested by an immediate skin reaction and in that the capacity for the reaction can be passively transferred. It differs, however, in that the individual is particularly reactive with a heat (60 C) labile product not involved in the reactions of the previous diphtheria-sensitive persons. This product is apparently contained in effective concentration only in the unheated culture filtrates of toxicogenic diphtheria bacilli and not in the filtrates of non-toxicogenic strains nor in solutions of material derived from the washed bacterial cells. If it is not toxin, it is a hitherto unrecognized diphtheria bacterial product that possesses a degree of lability not usually encountered among the

bacterial substances associated with hypersensitive reactions The results are discussed in respect to the possibility that the described reactions may represent an example of true hypersensitiveness of man to diphtheria toxin

AUTHORS' SUMMARY

THE INFLUENCE OF BLOCKADE OF THE RETICULO-ENDOTHELIAL SYSTEM ON THE FORMATION OF ANTIBODIES P R CANNON, R B BAER, F L SULLIVAN and J R WEBSTER, *J Immunol* **17** 441, 1929

The liberation into the blood stream of hemolysins to sheep's red corpuscles following blocking procedures depends on the manner of administration of the blocking material and the amount of antigen injected Repeated injections of suspensions of india ink particularly when given intravenously and continued after the injection of a small quantity of "tested-antigen," are followed by a significant decrease in the liberation of antibody into the blood stream, this liberation apparently varying inversely with the extent to which the phagocytic cells are blocked This decrease in output of antibody is independent of individual variation of animals, loss of weight or of depression by fluids alone Evidence is presented that small amounts of blocking material stimulate the liberation of antibody whereas large amounts tend to depress such a liberation These experiments offer additional evidence that antibodies, at least hemolysins, are formed by the phagocytic cells of the mesenchymal tissues

AUTHORS' SUMMARY

THE SENSITIVENESS OF TUBERCULOUS GUINEA PIGS ONE MONTH OLD TO THE TOXICITY OF TUBERCULIN JULES FREUND, *J Immunol* **17** 465, 1929

The intracutaneous tuberculin test is negative or only very slightly positive in tuberculous guinea-pigs not more than 1 month old Guinea-pigs of this age are about as sensitive to the toxin action of old tuberculin injected into the peritoneal cavity as adult tuberculous guinea-pigs These experiments indicate that the mechanism that mediates systemic hypersensitiveness is fully developed in young tuberculous guinea-pigs at an age when the dermal reaction is very slight or negative

AUTHOR'S SUMMARY

ON THE NATURAL IMMUNITY TO SCARLET FEVER OF THE JAPANESE AND CHINESE RESIDING IN SOUTH MANCHURIA K ANDO, H NISHIMURA and K OZAKI, *J Immunol* **17** 473, 1929

According to the Dick skin test there is a considerable difference in the susceptibility to scarlet fever between the Japanese and the Chinese residing in South Manchuria The difference in scarlet fever morbidity of these two races may at least be partly explained by the difference in their susceptibility No fact has been discovered which seems to indicate that there is a greater percentage of negative reactors among Japanese children who lived long or were born in Manchuria where scarlet fever is more prevalent than in Japan proper than among those who lived long in Japan proper and have immigrated only recently It seems reasonable to suppose that the difference in susceptibility may indicate racial difference of "Antikörperbildungsbereitschaft" in the sense of Hirszfeld, but not dependent on the difference in "Umwelteinflüsse"

AUTHORS' SUMMARY

ROCKY MOUNTAIN SPOTTED FEVER A L KERLEE and R R SPENCER, *Pub Health Rep* **44** 179, 1929

The serums from guinea-pigs inoculated with Rocky Mountain spotted fever virus did not agglutinate two strains of *B. proteus* X₁.

Serums from rabbits similarly inoculated with spotted fever virus showed a definite increase in agglutinin content reaching a maximum titer on the ninth day after onset of symptoms, or the fourteenth day after inoculation

The serums of human patients taken during the course of the disease and during convalescence showed the presence of agglutinins for two strains of *B. proteus* X₁₀

ALTHORS' SUMMARY

POSTVACCINAL ENCEPHALITIS E. GILDEMEISTER, Centralbl f Bakteriologie (Abt 1) **110** 120, 1929

This paper is a general discussion of the problem of postvaccinal encephalitis. The cases occurring particularly in Europe and England are reviewed and discussed. The view most stressed is that of the so-called activation theory, namely, that the vaccination activates an invisible virus already present in the body of the person vaccinated. No definite facts, however, are given to explain the phenomenon.

PAUL R. CANNON

THE INFLUENCE OF THE RETICULO-ENDOTHELIAL SYSTEM ON INFECTION AND ANTIBODY FORMATION WITH VACCINE VIRUS S. ZURUZOGULU and N. JOFFE, Centralbl f Bakteriologie (Abt 1) **110** 220, 1929

Guinea-pigs and rabbits were subjected to intravenous injections with india ink and then tested with vaccine virus to determine the effect on the local reaction and the formation of antibodies. The local reaction was less in the blocked animals than in the controls, whereas in the earlier periods, more virus was present in the blood stream of the blocked than of the control animals.

PAUL R. CANNON

THE EFFECT OF ROENTGEN RAYS ON THE SPECIFIC IMMUNE BODIES ALEXANDER LUSZTIG, Centralbl f Bakteriologie (Abt 1) **111** 244, 1929

The effects of roentgen rays on the specific antibodies depends on the intensity, the time of radiation with respect to the injection of the antigen and the individual reactivity of the animal. Thus, under certain conditions, there is an increased production of antibodies, while under others there is a reduction. The detailed results for various types of antibodies are given.

PAUL R. CANNON

CHANGES IN THE RETICULO-ENDOTHELIUM OF THE LIVER, SPLEEN AND LYMPH NODES OF IMMUNE RABBITS EMIL EPSTEIN, Centralbl f Bakteriologie (Abt 1) **110** 223, 1929

This is a morphologic study of the changes induced in the reticulo-endothelial cells of the rabbits immunized against swine serum, sheeps' red cells, etc., rather than against living infectious antigens. Thus, the changes are not complicated by the inflammation from infection. The experiments demonstrated particularly well in the liver an active proliferation of the cells of the reticulo-endothelial apparatus. The various types of such cells are described in detail and their possible sites of origin discussed. In the spleen and lymph nodes there was a marked proliferation of reticulum cells and a prominence of germinal centers in the malpighian bodies. He concludes that the noninfectious antigen acts on these cells of the histiocytic apparatus as an activating irritant, the cells reacting not only by proliferation but also by the secretion of antibodies.

PAUL R. CANNON

ENCEPHALITIS FOLLOWING SMALLPOX VACCINATION E. GILDEMEISTER, Deutsche med Wchnschr **55** 1372, 1929

The spinal fluids from four patients with postvaccinal encephalitis were examined for vaccine virus by inoculation into the corneas of rabbits. In one patient the

spinal fluid taken on the seventh day after vaccination was found to contain the virus, while the spinal fluids of the other three taken from twenty to twenty-four days after vaccination produced no corneal reaction

PAUL J. BRESLICH

PROTECTIVE SUBSTANCES IN SYPHILIS A. HAUPTMANN and A. GALLINEK, *Klin Wchnschr* 8 1485, 1929

The effects of normal serum (with and without phagocytes) on spirochetes was compared under identical conditions with the effects of syphilitic and meta-syphilitic serum (with and without phagocytes). The serum of ten normal persons, of ten patients with secondary syphilis, of eleven patients with paralysis, and of two patients with cerebrospinal syphilis was tested against spirochetes, all but in the last mentioned from chancres of rabbits. There was no difference in the effects of serum with and without leukocytes. Lethal effects of the spirochetes began with normal serum after three hours and were completed after five hours. In half of the serums from patients with secondary syphilis these manifestations began in ten minutes, and after thirty minutes the spirochetes were dead. In the remainder of the serums from patients with secondary syphilis the lethal effects began after from one to one and one-half hours and were complete after from one and one-half to two hours. In only one serum were there higher values. The patient from whom this serum was obtained was found later to have received antisyphilitic treatment. The serum of paralytic patients reacted practically like that of normal persons. Lethal effects with serum from patients with cerebrospinal syphilis appeared in a short time. In these experiments spirochetes obtained from cultures were used. With leukocytes present in this series the spirochetes remained alive for a shorter time than in serum alone.

EDWIN F. HIRSCH

THE PHYSIOLOGIC MALLEIN REACTION H. BROKMAN and H. HIRSZFELD, *Klin Wchnschr* 8 1499, 1929

The intracutaneous mallein test in a certain percentage of children is positive, and this percentage increases with age. The percentage range in the authors' series varies between 12.5 in the 0 to 1 year group and 42.3 in the 5 to 12 years group.

EDWIN F. HIRSCH

THE NORMAL HUMAN ANTIBODY CURVE E. FRIEDBERGER, G. BOCK and A. FURSTENHEIM, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 64 294, 1929

The blood serum of various ages was studied with respect to its content in lysin for sheep corpuscles and agglutinin for rabbit corpuscles. No such antibodies were found in the blood of the umbilical cord at birth, but during the early years the content in antibodies rises, reaching the high point at the age of 10 years, the lysin now diminishes henceforth while the agglutinin remains high until about the thirtieth year when a gradual fall begins. There are individual exceptions to this general course. The content of the blood serum in the antibody bears no relation to the blood grouping. The course of the antibodies in question resembles that of diphtheria antitoxin, and it is suggested that the antitoxin curve is not due to infection but to the manifestation of a general biologic phenomenon.

Tumors

THE AGE INCIDENCE OF TUMORS IN MICE AND ITS INHERITANCE L. J. TUREEN and LEO LOEB, *J. Cancer Research* 13 1, 1929

The present detailed investigation by Tureen and Loeb is a painstaking analysis of the age incidence of tumors in mice. In this study as in those previously reported by Loeb, evidences are produced to show that there exists a

definite relationship between tumor age and tumor rate. In general, the higher the tumor rate, the earlier the tumors appear and the lower the tumor rate, the later they appear. The authors also found that in addition to this relation, there exists another factor, i. e., a specificity of the age incidence of tumors in certain strains. Thus, there are strains with a high tumor rate which do not appear as early as certain other strains with a tumor rate not higher than they have. In certain cases strains with a low tumor rate may show an early tumor age due to the fact that a substrain may differ from the parent strain in the tumor rate but may inherit its characteristic tumor age. These two factors, according to the authors, interacting with each other, determine the age incidence of tumors in mice. Tureen and Loeb go into details concerning the strains with high, medium and low tumor rates, as to their age incidence of tumors.

B M FRIED

SKIN LESIONS AMONG TAR WORKERS H B WOOD, J Cancer Research **13** 54, 1929

Wood investigated the direct effect of tar on 88 tar handlers in municipal gas works, in coke by-products plants and in plants making briquettes. As a result of his investigation he found that workmen handling coal tar developed tar warts. Low temperature, distillate tar and petroleum tar, respectively, did not have any irritating action on the human skin.

B M FRIED

AGGLUTINATION PHENOMENA IN CANCER N WATERMAN and L DE KROMMEL, J Cancer Research **13** 60, 1929

The authors produce evidence to show that in man, mouse, rat and rabbit, there normally exists agglutinins for tumor cells. The property of agglutination goes hand in hand with the cytolytic properties of human serum toward neoplastic cells as demonstrated by Freund and Kammerer. It is interesting that umbilical cord serum lacks the properties of agglutination and of cytotoxicity of tumor cells. It is likely that these "factors" are acquired during extra-uterine life.

B M FRIED

A CRITICAL SURVEY OF EPITHELIAL TUMORS OF THE APPENDIX A A THIBAUDEAU and E M BURKE, J Cancer Research **13** 73, 1929

In a review of 3,746 appendices the authors have found 19 epithelial tumors in the appendix and adjacent small intestine, 12 of which were of the carcinoid type. In their material there was no definite connection between the tumor and the epithelium of the mucous membrane. The tumors did not recur after removal. They are not always associated with inflammatory changes in the appendix or intestine.

B M FRIED

TRANSPLANTATION STUDIES ON TUMORS ARISING SPONTANEOUSLY IN HETEROZYGOUS INDIVIDUALS LEONIL C STRONG, J Cancer Research **13** 103, 1929

According to the genetic theory devised by Strong, the fate of the implanted tumor tissue when placed in a given person (host) is brought about by a reaction between the host (determined by its genetic constitution) and the transplanted tumor cell (controlled by its genetic constitution). Tumor cells possess a specific individuality which is self-regulating, being transmitted from one cell generation to the next through the process of cell division.

In the present elaborate experiments Strong demonstrates the fact that the growth of an implant in a given person is controlled by the activity of certain physiologic host determiners derived from the zygote that gave rise to the person. In every case investigated in controlled stock the susceptibility and immunity to the implant were definitely inherited according to Mendelian principles. Trans-

mission of susceptibility to the growth of the implanted tissue has always followed the laws of Mendelian heredity. The simultaneous functioning of dominant multiple factors has ever been the type of inheritance, except in one case.

The author is of the opinion that the problem of neoplastic tissue is a problem of genetics and may eventually be solved by genetic methods. He believes that it is permissible to expect that by the use of the transplantation method, together with a full appreciation of genetic principles, some light may be thrown on the problem of the conversion of normal tissue into the neoplastic type.

B M FRIED

A STATISTICAL STUDY OF THE OCCURRENCE OF CANCER AND TUBERCULOSIS IN 11,195 POST MORTEM EXAMINATIONS. H A CARLSON and E T BELL, *J Cancer Research* **13** 126, 1929

Active tuberculosis is much less frequent in cancerous than in noncancerous subjects, and cancer is much less common in those with active tuberculosis than in those with no tuberculosis or with healed tuberculosis. But active tuberculosis is even less frequently associated with heart disease than with cancer, and cancer shows less association with heart disease than with active tuberculosis.

These results do not mean that active tuberculosis inhibits the development of both cancer and heart disease. They are due to the fact that the majority of persons with active tuberculosis have no other major illness and therefore the control (noncancerous, without heart disease) must always have a higher percentage of tuberculosis.

The authors did not find any statistical evidence to support the view that there is an antagonism between cancer and tuberculosis.

The only proper control for the association of active tuberculosis and cancer is the incidence of active tuberculosis in some other disease.

AUTHOR'S SUMMARY

ON REGRESSION IN TRANSPLANTED TUMORS IN MICE FREED OF WORMS. MILLARD C MARSH, *J Cancer Research* **13** 136, 1929

A mammary tumor spontaneous in albino mice has been propagated in long inbred individuals of the strain in which it arose. These mice have a chronic infestation, which extends indefinitely through ancestral generations, with intestinal nematodes, besides sporadic cestodes. Regression of the transplanted tumor is low.

A colony of mice from this strain was segregated and kept free from intestinal helminths during four years and thirteen generations of continued inbreeding. In these mice regression of the transplanted tumor is high. The difference appears mathematically significant.

AUTHOR'S SUMMARY

BLOOD CHOLESTEROL STUDIES IN CANCER. W L MATTICK and K W BUCHWALD, *J Cancer Research* **13** 157, 1929

There is a tendency in cancer to a hypercholesterolemia in the plasma, with little change in the corpuscles. Lecithin fails to show significant changes except for slightly lower values in the plasma. Total fatty acids show the most marked changes, being especially higher than normal values in the plasma, with a lesser but similar tendency in the corpuscles. From the authors' work it would appear that in cancer either fat absorption is increased or the utilization is decreased, with resulting accumulation of total fatty acids and fats, especially in the plasma.

B M FRIED

ON TRUE MIXED CARCINOMATOUS AND SARCOMATOUS TUMORS (SARCO-CARCINOMA) WITH REPORT OF A MIXED CARCINOMA-CHONDROSARCOMA OF THE THYROID OF A DOG ROBERT MASON and H GIDEON WELLS, J Cancer Research **13** 207, 1929

The authors report a case of a large mixed tumor arising in the thyroid of a dog. This consisted of a mixture of adenocarcinoma with osteoid sarcoma. There were many metastases in the lungs, some consisting solely of carcinoma, some solely of osteoid sarcoma and some presenting a mixture of both elements.

B. M. FRIED

ENDDIFFERENTIATION OF PRIMARY CARCINOMA OF THE BRONCHI AND LUNGS CARL VERNON WELLER, J Cancer Research **13** 218 1929

Weller investigated fourteen primary pulmonary cancers, thirteen of which were found in a series of 3,000 necropsies. In no instance could he trace the origin of the tumor from the "alveolar epithelium." It seemed clear that all types of carcinoma of the lung can take origin from bronchial structure.

The histologic picture of a particular neoplasm or of a particular portion of a neoplasm depended on the degree of enddifferentiation and should not, therefore, be used to determine histogenesis. The author gives a histologic description of the fourteen bronchogenic tumors with an ingenious attempt to correlate the various forms of carcinoma on a biologic basis.

B. M. FRIED

NO LEAD IN TUMOR TISSUE AFTER INTRAVENOUS INJECTION OF COLLOIDAL LEAD M. C. REINHARD AND K. W. BUCHWALD, J Cancer Research **13** 239, 1929

In order to determine the quantity of lead deposited in tumor tissue following the intravenous injection of colloidal lead, the authors used mice bearing spontaneous tumors. They used the commercial lead diarsenol or colloidal lead phosphate. The chemical was injected intravenously. With the method used, they failed to reveal any traces of lead in the tumor tissue.

B. M. FRIED

CARCINOMA OF THE CERVIX UTERI AND RELATION BETWEEN THE HISTOLOGICAL STRUCTURE AND THE RESULTS OF RADIATION A. A. THIBAUDEAU and E. M. BURKE, J Cancer Research **13** 260, 1929

The authors attempted to correlate the clinical evidences of malignancy by a given tumor with the histologic characteristics as revealed on microscopic examination. For that purpose they investigated twenty-eight cases of epithelioma of the cervix uteri for which the patients were successfully treated by irradiation and which have shown no evidence of recurrence for more than five years.

Their conclusions are that histologic grouping and indexes of malignancy are of limited value in prognosis in cases of epithelioma of the cervix uteri.

B. M. FRIED

LACTIC ACID FORMATION IN TUMOR TISSUE HELEN R. DOWNES, J Cancer Research **13** 268, 1929

The study by Downes is concerned with the investigation of the lactic acid-forming ability of several different kinds of human tumors and of transplanted animal tumors. The results obtained yielded "neither confirmation nor disproof of Warburg's contention."

B. M. FRIED

CARCINOMA GELATINOSUM OF THE PROSTATE A KLISSUROW, *Virchows Arch f path Anat* **268** 515, 1928

This type of prostatic tumor is rarely observed. The microscopic examination showed large masses of mucoid material with islands or strands of carcinoma cells here and there.

K Hosoi

INNERVATION OF TUMORS L HIRZOG, *Virchows Arch f path Anat* **268** 536, 1928

The innervation of 100 benign and malignant tumors and metastases was studied by means of the modified Bielschowsky method to bring out the axis cylinders of the nerves. In the majority of the tumors, nerves were frequently found in the stroma if the growth was not circumscribed. In all primary tumors with well defined borders, benign as well as malignant, nerves were never found. This was found to be true also in circumscribed metastases of carcinoma. Signs of proliferation of the nerves were seldom observed. The various structures described by others as nerve end apparatus most likely are a sign of regeneration. The relationship of the nerves to the tumor cells in the form of a specific nerve end apparatus was not observed.

K Hosoi

MALIGNANT UTERINE CHORIO-EPITHELIOMA R MEYER, *Ztschr f Geburtsh u Gynak* **92** 259, 1927

Conclusions are drawn from twenty-eight cases of chorio-epithelioma uteri. The tumor originates from fetal epithelial cells of the normal placenta at different periods, or from rests of hydatiform moles of different age and after longer or shorter retention. Chorio-epithelioma of long latency either is not recognized in time on account of slow growth (but not more than one or two years after the last pregnancy) or more frequently a more recent, abortive pregnancy is overlooked. Chorio-epithelioma observed late after menopause represents an incorrect histologic diagnosis. A chorio-epithelioma has no stroma of its own. The tumor cells proliferate under preservation of the cytolytic qualities of the normal chorionic cells. The maternal tissue may react against their growth by coagulation of the tissue, a process affecting also the tumor cells, or it cannot resist these cells and the tumor cells then dissolve the maternal cells. Transitional conditions may exist in the individual tumors. The causal genesis is unknown. The proliferation of lutein cells and the formation of ovarian cysts are secondary to the tumor formation. They are moreover absent in early cases and in old women. They may undergo spontaneous regression after removal of the hydatiform mole or the chorio-epithelioma. Surgical trauma represents a doubtful contributory factor. Over-nourishment of chorionic epithelial cells which became separated from the ovum is one of the blastogenic factors. The histologic diagnosis is not always possible, especially not during the first two months of pregnancy, as the ovum possesses at that period a trophoblastic membrane with numerous masses of proliferating chorio-epithelial cells. Even the histologic evidence of lysis of maternal tissue may represent a physiologic process at that time. A positive diagnosis from the histologic examination alone is impossible during this period. The tumor follows usually a hydatiform mole when it occurs in this period. A positive diagnosis is justified only if there is a marked proliferation of chorio-epithelial cells. After the second month a large mass of chorio-epithelial cells in uterine tissue is indicative of malignancy. Hydatiform mole is an abnormal proliferation of chorio-epithelial cells which is more marked at an early stage than in a late one. Its persistence is suggestive of malignancy. The diagnosis of a malignant condition is more difficult if a hydatiform mole is present than if it is not. Chorionic epithelial cells surrounded by fresh maternal blood stay alive. These cells, located intravascularly deep in the muscle, represent a factor of steadily increasing danger in

regard to malignant transformation, metastases and ectopic malignant transformation of these cells. In the presence of villi the prognostic evaluation of the epithelial proliferation rests first with the evidence of tissue destruction, secondly with the unusual amount of chorio-epithelial cells and with the presence of atypical forms. But atypical forms alone are not indicative of malignancy as they may be due to the continuous fresh blood supply which results in a hypertrophy of the cells. The existence of destruction of maternal tissue and its lysis is, however, an absolute proof of malignancy. The presence of tissue coagulation cannot be used in the interpretation of the histologic observations. Especially does the presence of large masses of syncytial cells point to malignancy. The stroma of the villi does not furnish any evidence for the diagnosis. The diagnosis of a malignant condition can often only be made with due consideration of all clinical as well as pathologic observations. The diagnosis is difficult, requires great experience and cannot always be made. Every hemorrhage after delivery, abortion and especially after hydatiform mole has to be regarded as suggestive of chorio-epithelioma. Histologic examination of all tissue removed or expelled under such circumstances is absolutely indicated and necessary. Nodes in the visible genital sphere are always suggestive of metastases. Metastases have to be regarded as malignant even if they do not show destructive growth. Curettage of the uterus may be ineffective in chorio-epithelioma if the tumor is located in the uterine wall. Repeated examinations of the uterus and ovaries are indicated for several months following removal of a hydatiform mole. Subsequent irregular hemorrhages demand curettage and histologic examination of the removed tissue. Benign metastases exist in hydatiform mole. They consist always of villi. The early surgical removal of a chorio-epithelioma gives the best curative results. The extirpation has to be carefully done to prevent the production of operative traumatic metastases.

W. C. HULPER

Medicolegal Pathology

CARBON TETRACHLORIDE POISONING WITH MACROSCOPIC FAT IN THE PULMONARY ARTERY. H. E. MACMAHON and SOMA WEISS, *Am J Path* 5 623, 1929

The gross and microscopic observations are described in an unusual case of carbon tetrachloride poisoning in which the blood in the right side of the heart and larger pulmonary arteries contained an extremely high percentage of fat (60 per cent). The severe damage to the liver, which was already large and filled with fat, was the probable source of the fat in the vascular system. Fat droplets that were small enough to pass through the capillaries of the lung and to gain entrance into the capillaries of other organs produced no microscopic lesions in either the heart, brain or kidney. It appears from these observations that the sensitiveness of alcoholic patients to carbon tetrachloride is increased not only because of increased absorption of the drug, as well as the synergistic action of alcohol and carbon tetrachloride together in producing liver damage, but also because of the possible presence of preexisting liver damage.

AUTHORS' SUMMARY

ACUTE YELLOW ATROPHY OF THE LIVER DUE TO ACETYLENE TETRACHLORIDE. W. SCHIBLER, *Schweiz med Wchnschr* 59 1079, 1929

Several cases of jaundice developed in workers in a shoe factory in which glue containing acetylene tetrachloride was used. In three cases death occurred. A detailed description is given of two of these cases in which acute yellow atrophy of the liver was present.

TATTOOINGS IN CRIMINALS DIAGNOSTIC VALUE PIETRO BIANCONI, Arch di antrop crim **49** 66, 1929

According to the Lombrosian school, tattooings not only contain important data for identification but invariably indicate a decreased cutaneous sensibility toward pain, peculiar to many criminals. Tattooings often disclose some important psychologic characteristics pertaining to the intelligence and to the sentimental and emotional life of the delinquent, and they may yield valuable information about the life of the criminal. Some tattooings betray criminal attitudes and tendencies, and thus illustrate the dangerousness of the persons. Nearly all tattooings are manifestations of an inferior and atavistic psyche, tending to materialize a dominant idea in the form of a symbol, which uncovers and represents the delinquent's way of feeling and simultaneously expresses a more or less pronounced imprudence. In two cases of offenses against property the tattooings are minutely described and psychologically interpreted.

E. L. MILOSLAVICH

SUBEPICARDIAL ECCHYMOSES IN ACUTE ASPHYXIA FRANCESCO BAILOTTA, Arch di antrop crim **49** 503, 1929

Following the observations of Bichart, Tullio and Busnco have recently shown by roentgenographic and cinematographic studies that during asphyxiation the heart dilates, at times to such a degree that it appears twice as large as under normal circumstances. The author studied the development of subepicardial ecchymoses, using the technic of these investigators. He confirms the observations of Hofman that minute petechial hemorrhages are found regularly in the asphyxiated newborn but are rare in adults. In experiments on rabbits and dogs Ballotta observed that at the beginning of asphyxiation the heart shows a decrease in size. This stage is followed by enlargement to about twice the normal size, occurring during the twenty-fifth to the thirtieth second of asphyxiation and lasting for approximately 20 seconds. Particularly the right ventricle seems to become dilated. Then a decrease in the volume of the heart again occurs. Subepicardial ecchymoses are not present. When the heart enlarges, during the stage of the acute asphyxia, its vessels also show dilatation and engorgement but do not rupture. However, subepicardial hemorrhages develop if the wall of the blood vessel possesses an insufficient elasticity. In the newborn, the vascular elastic apparatus is not yet completely developed, and in adults the wall of the vessel may be diseased. The occurrence of subepicardial hemorrhages depends, therefore, on the structural condition of the walls of the blood vessels.

E. L. MILOSLAVICH

Technical

A STUDY OF STOOLS CULTURED FOR *ENTAMEBA HISTOLYTICA* FOR DIAGNOSTIC AND OTHER PURPOSES CARLO J. TRIPOLI, Am J M Sc **178** 822, 1929

The cultural method of stool examination here described for the diagnosis of the presence of *Entameba histolytica* has so far been equal to any laboratory means of diagnosis and may eventually prove superior to the direct microscopic method. It is thought that the use of the cultural method of stool examination will result in a considerable saving of time and personnel in public health work in the detection of carriers.

JOHN PHAIR

AN EVALUATION OF THE LEUKOCYTIC REACTION IN TUBERCULOSIS E. M. MEDLAR, Am Rev Tuberc **20** 312, 1929

There is no specific leukocytic reaction in the tuberculous patient, and the use of the leukocytic formula is impossible as a diagnostic aid. The leukocytes may merely indicate that something abnormal is happening within the body. The

establishment of the clinical diagnosis of tuberculosis is necessary before the leukocytes can be of aid in the interpretation of the status of the tuberculous process. One may then interpret the leukocytic picture on the basis of the role that each leukocytic type plays in the pathogenesis of tuberculosis. The leukocytic reaction often agrees closely with the clinical status of a tuberculous person but at times there is a marked disagreement and then the leukocytes indicate the actual status of the tuberculous process more accurately than does the clinical condition of the patient. The leukocytes indicate only the status of the tuberculous process at the time the blood is obtained and therefore blood counts at relatively frequent intervals are necessary to determine the trend of the disease. It is essential that the total leukocyte count, together with the differential percentages, be used if the maximum information is to be obtained from a leukocytic reaction in a case of tuberculosis. The neutrophil plays the chief role in tuberculous abscess formation and in the extension of tuberculous ulcers. The mononuclear leukocyte is the chief cell in new tubercle formation, and the lymphocyte predominates when a tuberculous lesion is healing. No definite role can be ascribed, at present, to the eosinophil or basophil.

H J CORPER

PHOTO-ELECTROMETER WITH ONE STAGE OF AMPLIFICATION AS APPLIED TO THE DETERMINATION OF HEMOGLOBIN CHARLES SHLARD and A H SANFORD, J A M A 93 1951, 1929

The authors present the following. A description of a modification of our original photo-electrometer used as a photo-electric hemoglobinometer, in which we have employed one stage of amplification and used a micro-ammeter for the measurement of the current in the photo-electric cell produced by the illumination from a constant source of light which passes through a selective absorptive filter and a specified dilution of blood, the portability of the instrument and the accurate and rapid determination of hemoglobin expressed in grams for each hundred cubic centimeters of blood, which recommend the photo-electric hemoglobinometer as an instrument of value in the routine examination of a large number of samples of blood and in research work, complete details regarding the modus operandi of the photo-electrometer, the theoretical considerations involved in photo-electric photometry as applied to the determination of hemoglobin, indicating that the readings on the instrument follow the laws of Lambert and Beer, in that the concentration of hemoglobin, as determined by the transmission of light in an absorption zone of oxyhemoglobin (beta band), is proportional to the negative logarithm of the unabsorbed light, experimental data obtained by the van Slyke, spectrophotometer and photo-electric hemoglobinometer and their comparison together with a determination of the absorption ratios spectrophotometrically (at 540 millmicrons) and by use of the photo-electric hemoglobinometer, a selective filter transmitting light only in the region of the beta absorption band of oxyhemoglobin being used, data substantiating the belief that the photo-electric hemoglobinometer, with one stage of amplification, will permit of the determination of grams of hemoglobin for each hundred cubic centimeters of blood within an average of 2 per cent of the van Slyke values, which have been taken as standards, the applicability of the principles of photo-electrometry to the determination of amounts of various unknowns in true or colloidal solutions, provided the unknown substance in solution possesses at least one characteristic absorption band for which a spectral filter, transmitting radiant energy only in the specified region, can be made.

AUTHORS' SUMMARY

INFLUENCE OF FORMALIN FIXATION ON THE LIPOIDS OF THE CENTRAL NERVOUS SYSTEM ARTHUR WEIL, J Biol Chem 83 601, 1929

1 The present opinion that solutions of formaldehyde are a fixative for the preservation of lipoids should be revised

2 In a 10 per cent solution of formalin (4 per cent solution of formaldehyde) the phosphatides are hydrolyzed, and the liberated phosphoric acid is found in a water-soluble composition in the fixing fluid. This process of decomposition proceeded gradually and was still found after ninety days' fixation.

3 Cholesterol and galactolipids (cerebrosides) are not appreciably changed. Consequently the resulting mixture of lipids after fixation in formalin contains more galactolipids than the original tissue.

4 The preservation and relative increase of galactolipids in formalin-fixed tissue have been utilized to explain some empirically known histologic facts, namely, the effect of pyridine in silver staining methods of nerve fibers and the staining and physical qualities of areas of so-called "mucoid degeneration" which are found in formalin-fixed material after treatment with alcohol.

AUTHOR'S SUMMARY

THE DEMONSTRATION OF TUBERCLE BACILLI IN THE NEGATIVE SPUTUM OF TUBERCULOUS PATIENTS BY THE METHOD OF SCHILLER. R. MICHEL, *Beitr z Klin d Tuberk* **72** 513, 1929.

This method yields more positive results than the usual methods of concentration, but fewer than cultural methods.

MAX PINNER

PURE CARBON MONOXIDE GAS AS A BLOOD AND TISSUE-PIGMENT FIXATIVE. J. KERNER, *Centralbl f allg Path u path Anat* **46** 5, 1929.

Kerner prepares gross specimens of fresh tissue as for permanent mounting, suspends them in a bell jar into which pure CO is put and thus preserves the natural coloration. The final results were undistinguishable from those obtained by the standard, slower fixatives of Kaiserling, Melnikow-Raswedenkow, Piek or Jores. Subsequent preservation in formaldehyde or glycerin solutions does not affect the colors.

GEORGE RUKSTINAT

CULTIVATION OF THE TUBERCLE BACILLUS BY THE METHODS OF UHLENHUTH AND HOHN. GERHARD ORZECOWSKI, *Centralbl f Bakteriol (Abt 1)* **111** 362, 1929.

The method of Hohn yielded 96 per cent of positive cultures of tubercle bacilli, as against 39 per cent with the method of Uhlenhuth, in seventy-five sputums containing tubercle bacilli. For the microscopic examinations, however, the former method is not so satisfactory as the method of Uhlenhuth.

PAUL R. CANNON

THE APPLICATION OF HOHN'S METHOD FOR THE CULTIVATION OF TUBERCLE BACILLI IN SANATORIA. K. KRAUSE, *Ztschr f Tuberk* **54** 227, 1929.

This culture method yielded positive results in 234 per cent of 120 microscopically negative specimens of sputum.

MAX PINNER

THE PRACTICAL SIGNIFICANCE OF TUBERCLE BACILLUS CULTURES FROM SPUTUM. H. SCHULTE-TIGGES, *Ztschr f Tuberk* **54** 230, 1929.

Hohn's method for the isolation of tubercle bacilli yields many more positive results than bacterioscopic examination, but it is not as reliable as inoculation into animals.

MAX PINNER

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF GENITO-URINARY SURGERY

Stated Meeting March 6, 1930

JOHN A. HARTWELL, *Presiding*

CLINICAL APPLICATIONS OF THE STRUCTURE OF TUMOR OF THE BLADDER PAUL W. ASCHNER

This study was made on 285 cases of vesical neoplasm submitted to biopsy or operation at the Mount Sinai Hospital since 1911. The classification employed is in accord with the general principles of tumor terminology and meets the clinical requirements in that it takes cognizance of gross as well as microscopic criteria. It is as follows:

- I Papilloma (benign) cell uniformity and typism
 - Pedunculated single
 - multiple
 - Sessile papillomatosis
- II Papillary carcinoma
 - Noninfiltrating (a) scattered areas of somewhat atypical cells
 - (b) more diffuse, more marked atypism
 - Infiltrating (c) cells of benign type (rare)
 - (d) cells anaplastic, stroma or stalk invasion
 - (e) cells anaplastic, submucosal or base invasion
 - (f) cells anaplastic, muscularis and perivesical invasion
- III Nonpapillary (flat) carcinoma
 - (a) fibro (scirrhous)
 - (b) medullary (transitional cell)
 - (c) adeno
 - (d) squamous
 - (e) hornifying

There were two chief objects of the study, to evaluate the biopsy for diagnosis and to evaluate the structure in relation to prognosis.

The biopsy material is obtained with a rongeur forceps through the cystoscope. It is important to obtain material from different parts of the tumor and from various tumors when they are multiple. Tissue removed with the fulgurating electrode is unsatisfactory. The material must be studied with great care and attention to details, and with a mental attitude of "guilty until proved innocent."

In 242 cases the biopsy diagnosis rendered was correct in all but twelve, or 95 per cent. In reviewing these twelve cases, seven were found to be true errors, which could have been avoided. Therefore, the biopsy is potentially reliable in 97.5 per cent of cases (table 1).

TABLE 1—*Papilloma Biopsy Reports Confirmed, Ninety Cases*

Number of Tumors in Bladder	Confirmed by Early Cystoscope Control	Confirmed by Operative Specimen	Confirmed by Cystoscope Control (1 to 15 years)	Confirmed by Late Letter Control	New Tumors or Recurrences Benign, Only 23 per Cent
Single, 56 cases	29	6	26	1	12
Multiple, 25 cases	14	4	9		7
Papillomatosis, 9 cases	1	5	5	2*	2

* One autopsy five years after cure

The sources of error in biopsy diagnosis are

- 1 Insufficient material or improper material
- 2 Rare cases of infiltrating tumors of benign cell type (IIc)
- 3 Co-existence of benign and malignant growths in the same bladder
- 4 Malignant cell changes confined to inaccessible depths of the tumor
- 5 Cases of papillomatosis

It is of the utmost importance that biopsy be made before resorting to treatment for suspected malignancy because inflammatory lesions may closely simulate cancer. Failure to do this has led to harmful radical surgical intervention.

TABLE 2—*End-Results in One Hundred and Eighty-Two Patients with Tumors of the Bladder*

	Cases Followed up	Number Arrested	Percentage Arrested
Papilloma	60	48	80
Papillary carcinoma, noninfiltrating	21	9	43
Papillary carcinoma, infiltrating	71	17	24
Nonpapillary carcinoma	50	5	10

TABLE 3—*Summary of Two Hundred and Eighty-Five Cases Studied*

Type of Tumor	Number of Cases	Biopsy Done	Biopsy Errors	No Treatment	Cystoscopic Treatment	Operative Treatment	Operative Treatment plus Radium	Operative Deaths	Deaths Due to the Disease	Deaths Due to Other Causes	Benign Recurrence	Malignant Recurrence	Metastasis	Number of Cases Followed Up	Number of Cases Arrested	Percentage Arrested
Papillomas	91	90	0		71	23				4	22	1		60	48	80
Papillary carcinoma	138															
Noninfiltrating	30	25	5	5	9	11	5	5	5	4	1	2	2	21	9	43
Infiltrating	108	84	7	20	15	63	24	9	35	7	2	15	11	71	17	24
Nonpapillary carcinoma	44	35	0	10	1	29	4	9	15	1		9	6	30	5	16
Cases 6, 7, 9 and 10		4	2													
4 cases prostatic carcinoma		4	0													
1 myosarcoma																
1 adenoma																
1 carcinoma in scar after operation elsewhere																
1 fibroma																

Microscopic evidence of infiltration is found in 78 per cent of papillary carcinomas, whereas clinical signs of infiltration are observed in only 50 per cent. Resection should therefore include the full thickness of the wall of the bladder despite the absence of gross infiltration, whenever the biopsy reports papillary carcinoma and surgical intervention is resorted to. Failure to do so has resulted in early recurrence.

In 182 cases the termination of the case is known or a follow-up of three years is available. Cases with negative cystoscopy and with no evidence of metastasis are considered arrested. The results appear in tables 2 and 3.

Concerning prognosis, the following can be deduced. If cystologic criteria alone indicated prognosis there should be a marked difference between groups IIa and IIb, but the percentage of arrested cases was 44 and 42, respectively.

If infiltration of the wall of the bladder indicated prognosis, then groups IIc and III should show similar results, which is the case, the result being 14 and 16 per cent.

In comparing noninfiltrating papillary carcinoma (groups IIa and b) with infiltrating papillary carcinoma (groups II, c, d, e and f), the percentage of arrested cases is 43 and 18, respectively.

Papillomatous cases are treacherous, of thirteen, four eventually proved malignant.

Conclusions—Reliable information as to the nature of tumors of the bladder is obtainable by cystoscopic biopsy in 97.5 per cent of cases. The unavoidable failures occur chiefly in multiple tumors and papillomatosis.

Prognosis cannot be made from biopsy material alone in cases of malignancy.

A biopsy diagnosis of malignancy in a case simulating papilloma by cystoscopy and response to fulguration is a signal for more radical therapy (radium or surgical intervention).

Tumors of the bladder may be classified in a manner harmonious with general tumor terminology and with clinical requirements. They are benign or malignant.

Classification based on cell grading alone is not as practical for clinical purposes, and prognosis on such a basis does not coincide with the late results in this series of cases.

The presence or absence of infiltration appears to be a more reliable guide to the gravity of the situation.

The site of the malignant tumor determines its resectability and thus influences prognosis materially.

If a biopsy diagnosis of carcinoma is made and the case is considered surgical, segmental resection of the whole thickness of the wall of the bladder is the procedure of choice. Failure to do so even in the pedunculated tumors has often resulted in recurrence. Stalk invasion and tumor cells in blood vessels at the base cannot be detected by gross inspection.

As only thirty of 138 papillary carcinomas showed no evidence of infiltration, it is probable that types IIa and b represent an earlier stage in the development of the disease. Although histologic studies tempt one to believe that papillary carcinoma develops from papilloma in a considerable percentage of cases, the clinical evidence thereof is equivocal.

Before undertaking radical surgical intervention for tumor of the bladder a biopsy should be made, as other lesions may resemble neoplasm very closely.

A CONSIDERATION OF THE SURGICAL PROCEDURES IN THE TREATMENT FOR MALIGNANT DISEASE OF THE BLADDER. VERNE C. HUNT (Rochester, Minn.)

Considerable uniformity of opinion exists regarding the treatment for small single or multiple more or less superficial malignant lesions of the bladder. For the most part, such lesions have been and are at the present time successfully treated by transurethral electrocoagulation. Occasionally, however, there is failure of response to such treatment and other therapeutic agents as are applied to the larger and infiltrating lesions must be resorted to.

As yet there is still a justifiable conflict in the opinions regarding the relative merit of the physical agents and surgical procedures in some of the extensive malignant lesions of the bladder, and it is probable that in some instances the greatest prospects of cure and of palliation in the truly inoperable lesions may be expected through the combined use of both.

Experience has shown that some of the physical agents have been more effective in the treatment for the highly malignant lesions because of their greater radiosensitivity than the lower grade lesions. Other factors influence the results of treatment, however, not least of which is the extent of involvement. The lower grade lesions are often more or less superficial, while those of higher grade often infiltrate the entire thickness of the wall of the bladder with extravesical extension. Experience has shown that purely on the basis of the degree of malignancy one may be guided as to the justifiable magnitude of a contemplated surgical procedure, for with a given degree of involvement, the justifiable magnitude of surgical procedure is greater for the lower grade than for the higher grade.

malignant lesion At the present time, bearing in mind the optimism possessed by some regarding the results of treatment by physical agents, I am of the opinion that an operable malignant lesion of the bladder is a surgical lesion and is most successfully dealt with by surgical procedures

It may legitimately be asked What are the prospects of cure of malignant lesions of the bladder? A definite prognosis for a malignant lesion anywhere in the body in the individual case is practically impossible to make, and prognosis may be made only in general on the basis of previous experience Recently and elsewhere I reported the results obtained in the surgical treatment of 370 patients with graded epithelioma on whom all operations were done as procedures curative in purpose as opposed to palliative measures In brief, and in general, the results showed that irrespective of the size or situation of the lesion or the magnitude of the operation, 65 per cent of the patients on whom radical operations had been performed for lesions graded 1 and 2 lived three or more years without recurrence, as opposed to 34 per cent in whom the lesions were graded 3 and 4 who lived three or more years without recurrence When results were determined according to the site of the lesion, it was found that those following operations on the base of the bladder were not as good as those for lesions in the lateral walls and dome Actually the results showed that nearly 50 per cent more patients with lesions of the lateral walls and dome survived the three year period without recurrence than those who had been operated on for lesions of the base

Surgical Procedures—In a recent review of the surgical procedures employed during the years from 1925 to 1929 inclusive, in 256 cases of malignant lesion of the bladder at the Mayo Clinic it was found that in seventy-seven cases, or 30 per cent, the lesions were inoperable to any procedure that might be considered curative in purpose This includes patients in whom a cystostomy was done as a palliative procedure and those cases in which inoperability was ascertained on exploration, but does not include such cases as were clinically hopeless and in which not even palliative cystostomy seemed justifiable It is noteworthy that an additional seventy-eight cases were inoperable to the usual strictly surgical procedures of resection and excision, and comprised a group in which surgical diathermy, cautery destruction and transplantation of the ureters and cystectomy were undertaken A most conservative estimate places the inoperability or questionable operability in the neighborhood of 50 per cent, or, in other words, this estimate comprises those patients who, by virtue of the extensiveness of the lesion, if not entirely inoperable, may be treated, at best, with a poor prognosis

Tumors of the lateral and posterior walls and dome, by virtue of their situation, are most amenable to surgical excision and segmental resection, and in this situation these procedures offer the best prognosis

Tumors of the Base of the Bladder—Occlusion of one or both ureters by tumors of the base or their close proximity to the ureteral orifices and disposition of the ureters offer many obstacles to the successful treatment for tumors of the base of the bladder

Lesions surrounding, obstructing, involving or encroaching on one or the other ureteral orifice, or those in which the ureters are encroached on in the removal of the lesion, require some disposition of the ureter in addition to eradication of the growth Many such lesions may be hopefully removed by segmental resection, disposing of the ureter concerned by ligation or reimplantation into the bladder My experience with these two methods of disposing of the ureter has been reported Ascending infection presents the greatest hazard when reimplantation of the ureter is carried out, and in the series of cases at the Mayo Clinic previously reported the mortality for segmental resection and reimplantation of the ureter was 32 per cent as opposed to 13 + per cent for segmental resection and ligation of the ureter Even though the kidney the ureter of which has been permanently ligated may need to be drained or removed subsequently an account of an infected hydro-nephrosis, such procedures were necessary in only 10 per cent of the cases in the series from the Mayo Clinic

It would seem that the operation of cystectomy should have a wide field of application. However, this is not as yet the case, for in only a few instances are conditions such that cystectomy may be considered wise. Usually when the lesion is unsuitable for excision, resection, surgical diathermy or other physical agents, cystectomy is out of the question because of extravescical extension, remote metastasis, unilateral or bilateral partial or complete ureteral occlusion by the lesion or the poor condition of the patient. The magnitude of the operation of cystectomy with the simultaneous or preliminary disposition of the ureters is such that few patients with an extensive malignant growth of the bladder are suitable subjects for the procedure.

The disposition of the ureters has contributed greatly to the difficulties of the operation. Preliminary ureterostomy to the loin or inguinal area has facilitated subsequent cystectomy and has increased the safety of the operation, but presents the disadvantage of absence of a urinary receptacle. A number of cases have been reported in which the ureters have been transplanted into the sigmoid or rectum simultaneously with cystectomy, an operation that is accompanied by an extremely high mortality. The introduction of ureteral catheters into the ureters and bringing them out through the cystectomy wound or to the surface of the skin simultaneous with cystectomy has been a hazardous procedure because of ascending infection to the kidneys.

The perfection by C. H. Mayo and Coffey of methods of transplanting the ureters into the sigmoid has paved the way to the greater safety of cystectomy.

Beer recently reviewed the subject of cystectomy, presenting the advantages and disadvantages of the various methods of treating the ureters. Certainly the operative survival of seven patients whose cases were reported by him, from two months to as long as five years in one patient, represents an accomplishment which to my knowledge has not been equaled by any other method of cystectomy and simultaneous or previous disposition of the ureters.

DISCUSSION

JAMES EWING. This meeting demonstrates the importance of joint meetings between pathologists and clinicians. One might say that our clinical friends qualify for membership in the Pathological Society, first, at one extreme, owing to the great detail and accuracy with which clinical judgments have been based on thorough microscopic examinations, encouraging the pathologists to make these fine distinctions in the histologic study of tumors. And second, I think that the clinicians in this field deserve at least honorary membership in the society for having furnished us so much autopsy material from unexpected sources and so many tumors of the bladder under conditions in which we do not ordinarily obtain them. Our clinical friends might qualify as pathologists from both these points of view, and I wish that I could say as much for the pathologists. I do not think that pathologists are sufficiently acquainted with the clinical significance of some of the finer questions arising in the structure of tumors of the bladder to warrant being raised to the rank of genito-urinary surgeon. I trust that the demonstrations made here will encourage pathologists to learn more about the clinical aspects of the diseases with which they have to deal.

I was particularly interested in Dr. Aschmer's classification and his minute discussion of the anatomic features, and I am in accord with his general point of view. He recognizes the simple benign papilloma as a strictly benign tumor. In another tumor, which is grossly a strictly papillary tumor, there are peculiar groups of atypical cells and in these he finds that the clinical history often indicates a malignant course, and therefore he calls this tumor a papillary carcinoma. I doubt if all papillomas showing these occasional groups of atypical cells run a malignant course, and I would prefer to class them as simple papilloma, while noting the increased possibility of recurrence associated with these atypical cell groups. Then he has a type of papillary tumor that is definitely atypical throughout, but not necessarily infiltrating the base, which he also calls a papillary carcinoma.

It seems to me that there is a marked difference between this group and the simple papilloma with atypical cell groups, and I would prefer to separate sharply between them, applying the term carcinoma only to the latter. Pathologists do not like to call a process "cancer" unless it shows definite histologic criteria of carcinoma, such as markedly atypical cells, loss of polarity and heterotopia, which signs are missing in the simple papilloma with scanty groups of atypical cells. Then he has others more advanced, malignant and atypical throughout and definitely infiltrating the stalk and the wall of the bladder, and he makes a separate classification of all of these. Finally, he has the flat carcinomas, which are generally infiltrating. I think that there is much practical advantage in making these distinctions, but whether there is any theoretical ground for separating them so minutely I am inclined to doubt. While I agree with Dr. Aschner that tumors starting at one tempo do not often become transformed into more malignant tumors, in a group of 100 tumors of the bladder you will find many stages between benign papilloma up to malignant carcinoma, and in the individual cases it is often difficult to apply these special terms satisfactorily. I do not think that it is wise to assume that carcinoma is something entirely different from a malignant papilloma. The two types of disease tend to run into one another, not that one case becomes transformed into the other, but that different cases cover all of the gradations between one class and the other. The attempt to emphasize great differences between a solid carcinoma and a malignant papilloma is therefore strained. Nevertheless, it is most significant that by this careful histologic analysis of tumors of the bladder, which I believe has been carried out more particularly in Mount Sinai Hospital than elsewhere, they have been able to show that the presence of these small groups of atypical cells in an otherwise benign papilloma carries with it an increased gravity in prognosis, and that is a significant thing for the pathologist. It encourages us to make more minute studies of histologic preparations, and to express opinions regarding the clinical course of the disease which we are as a rule loath to make, because the prediction of the clinical course of any tumor from the histologic section is always more or less hazardous. I do not know that there is any other field in tumor pathology in which such significance may be attached to the histologic structure. Possibly it is found in the larynx also. I have long since noted that the presence of a few atypical cells in a papilloma of the larynx generally signifies that the disease will recur and will kill the patient sooner or later. Pathologists may be encouraged to apply these criteria more carefully in other fields.

The question of histologic grading has long interested me. I am in favor of histologic grading carried as far as possible. While we have been grading tumors ever since the microscope has been used, the tendency to grade tumors more carefully has been increasing recently, owing to the work of Broders. I have little sympathy with the pathologists who, because of lack of knowledge or intellectual laziness, discard the matter of grading tumors as of no value and unsound. As industry increases and experience enlarges, most of these men will gradually see that they are finding an opportunity to serve the clinicians, which they should embrace under all circumstances. Therefore, I am in favor of the effort to grade tumors of the bladder, and we have had some satisfaction in our institution in this attempt. As I understand, Broders included in his group I of carcinomas of the bladder tumors that most pathologists call benign papilloma. His group II would probably fall in Dr. Aschner's class of papilloma with malignant cell groups. Therefore, we can readily understand why Broders' classes III and IV are the most numerous among the cancers of the bladder and are the malignant ones. We have found that there is considerable difference in the outcome of these four classes, but when it comes to making fine distinctions between groups III and IV, the true carcinomas, the clinical significance is perhaps not as great as it is in some other tumors, but it is still of value.

Another interesting point for the pathologist to keep in mind has been brought out by Dr. Hunt's remark that the malignancy of tumors in the bladder varies according to the location, the more malignant tumors being located in the trigone

and the less malignant ones at the fundus. This is also true of tumors of the alimentary tract, which increase in malignancy from the anus to the lips. These tumors vary in malignancy depending on location. In our head and neck service we are beginning to lay considerable stress on the location of a tumor, which in some instances seems to determine more or less the malignant course, even when it is of the same histologic structure as tumors located elsewhere which prove to be more benign. This again is a lesson which the clinician teaches the pathologist.

While the clinicians deserve membership in the Pathological Society because they have largely taken over the work of the pathologist, they have neglected some questions that are strictly clinical. I have not heard a word about the causation of cancers of the bladder. I have heard nothing about the importance of the age distribution in carcinoma of the bladder. I should like to know something about the general constitution of these patients and the previous history of the bladder. Has not the chemical analysis of the blood given some important information on this subject? If not, then it is the only subject in which it is not claimed to have made an important contribution. All of these questions belong in the realm of the clinician, and the clinicians seem to have left most of them for the pathologist to follow up.

EDWARD L. KEYES. I am not qualified to elucidate any further the differences in cellular malignancy. Although certain minor differences in opinion have appeared, we all agree on the important things, such as the use of the biopsy and the grading of tumors in one way or another. However, you will notice that there is great confusion in the fundamental use of the word malignancy. In both of the lists of statistics that have been shown, malignancy has been ultimately graded apparently in accord with the prospect of the death of the patient, as a result either of his tumor or of the treatment or lack of treatment. It is extremely difficult to disentangle these two items—the malignancy of the tumor itself and the malignancy of the surgeon who treats the tumor, or the lack of treatment that the tumor gets. Surely even a true carcinoma of the bladder may, if seen early enough, some times be controlled by relatively benign treatment. I have seen one such case, a primarily infiltrating tumor of the bladder, which I watched arise from beneath the mucosa and come through it, and that tumor has been controlled for several years, after the implantation of radium seeds through the cystoscope.

We should seriously push to the extreme limit in expert hands those methods of attack which are the least malignant. It is because of the lack of malignancy of the suprapubic operation for the implantation of radium that that method of approach has especially appealed to me. I will not quote statistics. In my hands the implantation of radium suprapubically has given me an operative mortality of less than 10 per cent. In other words, I have been less malignant than Dr. Hunt has. (I have perhaps been less efficient also. In certain individual cases it is impossible to compare results.)

I have been greatly interested in the use of diathermy, which again is a non-malignant method of treatment as compared to the radical methods which he, like other surgeons, used to employ. There is a general tendency, I think, on the part of the surgeons to become less malignant. I believe that it is along these lines that we shall progress, but we have a long way to go in weighing the advantage of cauterizing these tumors by the different physical agents, the electrocautery in contrast with radium. I favor the use of radium. I am not prepared to state that I have any facts to prove that my favoritism is justified.

BENJAMIN S. BARRINGER. You have heard both Dr. Aschner's and Dr. Hunt's careful and illuminating papers on the structure and surgical treatment of tumors of the bladder. I am personally much indebted to them for these papers. Rather than discuss Dr. Hunt's paper directly, I believe that it will fill out the picture to a certain extent to give the results of the treatment for cancers of the bladder by radium. Surgery and radium have long been contestants in the race for supremacy, and no one can say at present which will win. The comparison between results from radium and surgical treatment is difficult because surgery picks the

cases which are operable and discards the rest. At the Memorial Hospital we have subjected to irradiation every patient with cancer of the bladder in whom the cancer was believed to be confined to the bladder, no matter how large the tumor might be. Therefore, in our series are included many inoperable cases. Sixty-three and five-tenths per cent of the tumors involved were adjacent to the trigone, including in the growth one or both ureters or the internal urethral orifice. Twenty-eight per cent of the tumors had bases of 6 square centimeters (1 square inch) or less. In 72 per cent the bases of the tumor were greater than this, many of the tumors involving one half or one third of the wall of the bladder.

In the slides showing the result of radium implantation it is seen that the clinical diagnosis is often at variance with the anatomic diagnosis. This is unavoidable, as we have to be content with a small portion of the tumor for the histologic examination. Under these conditions the clinical diagnosis is more accurate than the microscopic diagnosis. For example, a microscopic diagnosis of a papilloma of a sloughing tumor has to be modified. A microscopic diagnosis of papillary carcinoma of a tumor the base of which is felt to be indurated and into which base a radium-bearing needle makes way as though going through gristle likewise has to be modified. This is an infiltrating carcinoma.

In this first group of slides I show sixty-two cases of carcinoma of the bladder that have been graded by Dr. Ewing and Dr. Stewart according to their malignancy and radiosensitivity. The diagnosis has been purely microscopic and not clinical.

The second group of slides shows the results of treatment in ninety-five cases, divided according to the older classification into papillary and infiltrating cancer. The diagnosis has been entirely from the microscopic side, leaving out of consideration the clinical diagnosis. The clinical diagnosis has at times been at variance with the microscopic diagnosis. No papillomas have been included in these series. They have been rigidly excluded. All of these tumors have been epithelial tumors.

The first series of slides consists of graded tumors. The number of cases is too small to be of much importance. The first is a papilloma with atypical cells, fourteen cases. We controlled eight cases, or 57 per cent, and the uncontrolled number was six, or 43 per cent. These are papilloma with atypical cells. The result of treatment shows that these tumors are real malignant tumors.

The second slide shows the papillary carcinoma, group I, 40 per cent of which were controlled, and 60 per cent uncontrolled.

The third is the papillary carcinoma, group II, of which 50 per cent were controlled and 50 per cent uncontrolled.

The fourth slide shows grade 3 of the papillary carcinoma, and while it is not shown in the classification, it has been of a great deal of interest to me that when we get to grade 3 the age of the patient begins to fall below 50, which of course should always be a clue in the history as to the possible gradation of the tumor concerned. In the more malignant cases, and here again the number of cases is too small to be of any real significance, the controlled cases comprise 37 and the uncontrolled 62 per cent.

The infiltrating carcinoma, group I, which includes four cases, shows a drop in the controlled cases, 25 per cent against 75 per cent uncontrolled. An interesting case is one that I have included several times in my control cases, and in which the patient lived for nine years and finally died of the infiltrating carcinoma.

The next group is infiltrating carcinoma, grade 2, comprising eleven cases, 27 per cent were controlled and 73 per cent uncontrolled.

The next group is infiltrating cancer, grade 3, comprising four cases, 50 per cent were controlled and 50 per cent uncontrolled. In this group of cases of grade 3 malignancy the ages begin to fall below 50, while in the other two groups there have been none below the age of 50.

I want to point to the value of classifying the tumors according to their malignancy. It enables a more accurate comparison of results. That is what we are all after. When we wish to compare our results, if we have graded tumors we

can more accurately compare them and know what each investigator is talking about. The grading determines the radiosensitivity of tumors, and therefore the proper dose of radium to be used. Radiosensitive tumors to be removed by operation or radium probably should be subjected to irradiation by deep therapy before the operation. The grading also gives some idea of the prognosis of a tumor.

The second set of slides shows the results of treatment in ninety-five cases, divided according to the older classification into papillary and infiltrating carcinoma. The diagnosis has been entirely from the microscopic side, leaving out of consideration the clinical diagnosis. There were fifty-one cases of papillary carcinoma, twenty-seven cases, or 52.9 per cent, were controlled, twenty-two cases, or 43 per cent, were controlled for more than three years, and 47.1 per cent were not controlled.

There were forty-four cases of infiltrating carcinoma, nineteen cases, or 43.1 per cent, were controlled, fourteen cases, or 31.8 per cent, were controlled for more than three years, and twenty-five cases, or 56.9 per cent, were not controlled.

The third set of slides shows the results from radium in 125 cases in which the diagnosis was from the clinical side. This diagnosis has at times been at variance with the microscopic diagnosis. There were forty-five cases of papillary cancer, thirty cases, or 66 per cent, were controlled and twenty-five cases, or 55.5 per cent, were controlled for more than three years. Of eighty-two cases of infiltrating cancer, thirty, or 36.5 per cent, were controlled, twenty-three, or 27.8 per cent, were controlled for more than three years, and fifty-two, or 63.5 per cent, were not controlled.

Finally, I shall stress the decided difference between the operative mortality when a tumor is removed by surgical procedures and when it is implanted by radium. In 108 consecutive cases of suprapubic implantation of radium, four patients died in the hospital, an operative mortality of 3.7 per cent. This includes all cases, small and large, in which the tumor was thought to be confined to the bladder. In 62 per cent of these cases the tumor touched some part of the trigone, the ureters or the internal urethral orifice. In those cases in which the tumor could have been removed surgically and there were many in which it could not, the operative mortality would have been from 15 to 20 per cent in the most competent hands.

PAUL W. ASCHNER. I hoped that I had made myself clear. I do not like the term "malignant papilloma," and I did not use it. It did not appear in any of the tables, and it was mentioned only as one of the great sources of confusion. We diagnose cases as papilloma, as papillary carcinoma, noninfiltrating, as papillary carcinoma, infiltrating and as nonpapillary or flat carcinomas. When the pathologist reports a biopsy specimen as grade I in Broders' terminology, he certainly takes a great load off his own shoulders, because this grade of tumors includes both the cases which we recognize as benign papillomas, and some of those which Dr. Ewing and I recognize as definitely malignant tumors.

Dr. Barringer's interesting tables will no doubt prove of much value. However, I wish to point out that the diagnosis of infiltrating carcinoma is not purely a microscopic diagnosis. It is also a gross or a clinical diagnosis. The papillary carcinoma may or may not infiltrate. The flat carcinoma usually infiltrates.

The things that I want to stress are the accuracy of the biopsy in arriving at a diagnosis of malignancy, our inability to draw conclusions as to prognosis from biopsy alone and our belief that cytology alone is insufficient for grading tumors. I feel sure that when Dr. Ewing grades his tumors he is not guided by cytology alone. Certainly the clinician feels that the location of the growth and the extent of infiltration are of equal or greater importance in prognosis.

VERNE C. HUNT. I again want to repeat what I said in closing, that cancer of the bladder is still a very serious disease. I think that there is room for improvement in the results, and I think that the only way that such improvement will occur is through a comparison of the results obtained in definitely graded lesions, graded microscopically, and through a comparison of the results obtained

by the various therapeutic methods that are employed—surgical intervention, the various physical agents and what not—which calls to my mind again what Dr Keyes and I were talking about this noon. He recently sent out letters to the effect that all tumors of the bladder be examined in various clinics and be sent into the registry to be gone over, so that a definite classification of the tumors of the bladder may be accepted, if such a thing is possible. First of all, before we can obtain accurate results and compare the relative merit of the various therapeutic agents used, the surgeon, the pathologist and the clinician must talk the same language. That can be accomplished only through the registry that has been formulated, so that these tumors are examined at a certain place and by certain men and some degree of agreement is arrived at.

I had hoped that there would be some discussion regarding the structure of these lesions. You have heard about papillary carcinomas and infiltrating carcinomas, and I have been talking about epitheliomas. The reason I talked about them is because I talked with Dr Broders at the Mayo Clinic before I came here. I called him up and said, "You have told me this before, and as I have gone over the records I find that the tumors of the bladder are epitheliomas. Is it true that 95 per cent of the bladder tumors are epitheliomas?" He said, "They are." Other pathologists look at them as carcinomas. We must get together so that we all talk the same language. When that is accomplished, we can then begin to determine the relative merit of various physical agents, surgical procedures and so on, and not until then. I think that only through the comparison of methods can we learn. The future is open. I think that we are making progress.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, March 13, 1930

BALDUIN LUCKE, *President, in the Chair*

FIBROMYOMA OF UTERUS WEIGHING ONE HUNDRED AND THIRTY-THREE POUNDS REMOVED AT OPERATION. MOSES BEHREND

Mrs. A. P., aged 35, was admitted to Mount Sinai Hospital, on March 3, 1930. She said that nine years previously she was seized with sharp abdominal pain in conjunction with her menstrual period. About that time she noticed a small swelling in the lower part of the abdomen which had become progressively larger up to the time of presentation. She had walked and had worked as a druggist up to six weeks before presentation. She complained of thirst and dyspnea, but no urinary symptoms, and the bowels were regular. Menstruation began at 13, was always regular and was not painful. She had menstruated about three times in the past three years. Notwithstanding the size of the tumor, she said that she enjoyed good health, with the exception of weakness for the last six weeks. She had never been pregnant.

The abdomen was greatly enlarged, measuring 5 feet 8 inches (172.7 cm.) in circumference. The skin over the abdomen and the legs were edematous. Hard masses were felt on the lateral sides of the abdomen, with soft areas here and there. The mass was painless. On March 3, a tumor weighing 133 pounds (60.3 Kg.) was removed.

A GIANT CELL TUMOR WITH METASTASES OCCURRING IN A CHACMA BABOON, PAPIO PORCARIUS. HERBERT L. RATCLIFFE

A case of giant cell tumor occurring in a Chacma baboon is described. The growth originated near the lower epiphysis of the ulna, perforated the shaft and articular cartilage and infiltrated surrounding tissue. The development was rapid,

the tumor being discovered about three months before the animal was killed. At autopsy, metastases were found in the lungs, heart and gluteus muscles. An attempt to transplant this tumor to two rhesus monkeys failed.

MENINGOCOCCUS MENINGITIS ASSOCIATED WITH A GRAM-NEGATIVE BACILLUS A. I. RUBENSTONE and I. DAVIDSON

A girl, aged 12, was admitted to Mount Sinai Hospital in August, 1929, with clinical signs and symptoms of meningitis. The spinal fluid contained 1,450 cells, with 95 per cent polymorphonuclears. The direct smears of the spinal fluid showed gram-negative bacilli and diplococci, mostly intracellular. The diplococci proved culturally to be meningococci. The bacilli were motile organisms which stained characteristically darker at the ends. They produced acid and gas in dextrose, mannite, xylose, maltose, levulose, rhamnose and blackened lead acetate. They did not ferment lactose, saccharose, raffinose, salicin, arabinose, dextrin, dulcitol and inositol. Indol was not produced. Gelatin was not liquefied. In Russel's medium, the slant was alkaline and the butt acid, with a slight formation of gas. The milk was not coagulated. The reaction was slightly acid during the first forty-eight hours, then it became alkaline and remained so during the observation time of fourteen days. The organism was so placed in the group of *Salmonella* but it differed slightly from any known member of that group. Cultivation on the synthetic mediums of Pech and Kortenhaus did not help to identify the organism. Also agglutinations, absorptions and cross-agglutination tests did not place the organism in a definite subgroup of *Salmonella*. It probably belongs to one of the irregular members of that group.

The same organism could not be found in any other part of the patient's body. The patient's serum agglutinated it completely in a dilution of 1:30 and partly in a dilution of 1:50, while normal control serum produced only a partial agglutination in a dilution of 1:4. From the finding of the organism intracellularly in the direct smears jointly with a meningococcus and from the agglutination reaction with the patient's own serum, it is concluded that a mixed infection of the meninges was present. The patient was treated with antimeningococcus serum. She recovered within thirty days.

CHANGES IN THE SKIN REACTION TO HISTAMINE OCCURRING IN THE COMMON PERIPHERAL VASCULAR DISEASES. ISAAC STARR, JR.

The changes in the skin reaction to histamine have been studied in the common peripheral vascular diseases. The reactions above the knee or the wrist were always normal, those distally varied as follows. In diabetic arteriosclerosis (100 cases) the observations permit the classification of the patients as follows. Group 1. Pulsation in the peripheral arteries obliterated, histamine reaction delayed and incomplete. This is interpreted as indicating obliterative arterial disease without collateral compensation. Group 2. Peripheral pulsation obliterated, reaction normal, suggesting obliterative arterial disease with complete compensation by collateral circulation. Group 3. Peripheral pulsation present, histamine reaction delayed and incomplete, suggesting a pathologic condition in the smaller arteries. The frequent absence of flaring in the presence of whealing in this group demonstrates the great frequency of peripheral neuritis in diabetes. If gangrene is present in the feet, all reactions below the knee are usually abnormal.

In advanced nondiabetic arteriosclerosis (thirty cases), the reactions of the skin of the feet to histamine are usually incomplete or delayed unless hypertension is present. If the blood pressure of a patient who shows normal reactions when hypertensive falls to a normal level, the histamine reactions become delayed or incomplete, returning to normal as the blood pressure rises to its previous level. These observations demonstrate the importance of hypertension in compensating for sclerotic changes in the arteries.

In Buerger's disease (five cases) the reactions are normal down to a certain level, below which they become markedly retarded or incomplete. This level is

located on the distal part of the foot in early cases, it is higher in later ones. The flares are well preserved, often being present when whealing is absent.

In embolism of an arm or leg (three cases), the reactions gradually become more abnormal as one goes distally from the location of the embolus. There is no sharp line of change at the level of the embolus.

In Raynaud's disease (five cases), the reactions to histamine vary with the conditions of the vessels, being incomplete during periods of arterial spasm and normal when spasm is absent.

In achrocyanosis (two cases with redness but no pain), the flares in the involved area are higher and appear more promptly than in normal persons. The wheals are normal.

In one case of scleroderma of the hands, the reactions on the involved skin were normal. In a second case complicated by advanced peripheral arteriosclerosis, the reactions were normal on the involved skin of the face, trunk and proximal parts of the limbs, but became progressively more abnormal distal to the elbows and knees.

EXPERIMENTAL HYPERSENSITIVENESS TO DERIVATIVES OF PNEUMOCOCCUS LOUIS A. JULIANELLE

From this series of studies concerning the reactions of rabbits to injections of pneumococci and their products, it appears that when heat-killed pneumococci or their products are repeatedly injected into rabbits, intravenously or intracutaneously, the rabbits become hypersensitive to subsequent intracutaneous injections of pneumococcus proteins, as shown by a reaction in the skin, which is analogous to the phenomenon of Arthus as exemplified in rabbits following injections of nonbacterial protein. The development of this hypersensitiveness occurs simultaneously with the development of species-specific antibodies in the blood, and this type of hypersensitiveness may be transferred to normal rabbits following the transfer of blood serum from the sensitive animals. The development of this type of sensitivity seems to bear no relation to active immunity, since animals repeatedly given injections of soluble products of the pneumococcus cells show no active immunity, but nevertheless are skin reactive.

When the whole, killed bacteria are repeatedly injected intracutaneously, another type of hypersensitiveness, in addition to that just described, makes its appearance. This is shown by the fact that animals treated in this way react in a different manner to the individual injections of the bacteria into the skin. At the first injection a reaction occurs in the skin, a primary reaction, which disappears after a few days, but is followed in about ten days by a recrudescence. This recrudescence occurs even without a second injection, and is probably an evidence of the development of hypersensitiveness.

With repeated intracutaneous injections of the whole organisms, the skin reaction gradually becomes more severe, secondary reactions occur, however, only after the first injection. After from four to six injections have been made into the skin, the reactions become of lessened severity and are also modified in character. During the course of injections, therefore, the skin reactions are probably different from unmodified Arthus reactions, although the Arthus type of sensitivity is coincidentally present in the animals, as is shown by their exhibition of typical Arthus reactions when they are given injections of small amounts of pneumococcus protein twenty days later. That another type of sensitivity develops in these animals is also shown by the fact that they become eye sensitive to pneumococcus protein, while animals treated in other ways never do. Apparently, when bacteria are localized in the skin, a new and different kind of hypersensitiveness develops.

The reactivity manifested by the eye was found to be unrelated to type-specificity or to the formation of circulating antibodies. Unlike the reactivity of the skin to pneumococcus protein, the reactivity of the eye is not transferred to normal rabbits following the transfer of blood from sensitive to normal animals. While the skin reactivity occurs in resistant and nonresistant rabbits, the eye reactivity has been observed only in animals resistant to infection.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

CARL V. WELLER, *Secretary**University of Chicago, March 27, 28 and 29, 1930*WILLIAM F. PETERSEN, *President*BACTERIOLOGIC AND SEROLOGIC OBSERVATIONS IN BRUCELLA ABORTUS INFECTIONS
M. H. SOULE, UNIVERSITY OF MICHIGAN

These studies were undertaken to evaluate the presence of blood serum agglutinins and blood stream infection in relation to milk agglutinins and milk infection. The tests were made on more than 5,000 ordinary herd-run cows used for the production of milk. The animals were distributed as follows: 2,032 in Wisconsin, 1,736 in New York and 1,664 in Michigan. Two series of tests were made on each animal at intervals of approximately six months. The blood serums were tested for agglutinin content in dilutions of 1:50, 1:100, 1:200, 1:300 and 1:500, against living suspensions of *Brucella abortus*, strain 80. The blood was cultivated for *Brucella abortus* by the addition of 50 cc samples of blood to 450 cc volumes of sterile glycerol infusion broth and subsequent incubation in air enriched with carbon dioxide. The blood was diluted as soon as withdrawn and was not chemically treated or defibrinated to prevent clotting. At two to four day intervals, samples were removed and streaked on the surface of glycerol infusion agar. No blood samples were considered negative previous to six weeks' incubation. The presence of agglutinins in the milk was detected by taking 20 cc samples from each quarter of the udder, treating them with rennet and then using the clear milk serum, in the dilutions given, for the blood serum tests. *Brucella abortus* was isolated from the infected milk by the injection of 5 cc samples of milk from each quarter of the udder into the peritoneal cavity of guinea-pigs. At the end of five weeks the guinea-pigs were killed. If the spleens showed enlargement with tubercle-like lesions they were cultured on glycerol infusion agar, in air plus carbon dioxide. In the first series of tests agglutinins were present in the blood stream of 2,237 of the animals, but only 299 gave positive blood cultures. In the second series of tests agglutinins were present in 2,607 cases with 206 positive blood cultures. There were 40 positive blood cultures without concomitant blood agglutinins. The milk samples showed a greater parallelism between agglutinin content and milk infection. In the first tests 1,219 milk serums contained agglutinins with 1,143 positive cultures for *Brucella abortus*. The second series gave 1,544 positive agglutinin tests and 1,367 positive cultures. There were no positive cultures in samples free from agglutinins. There were 156 positive milk cultures in the first tests without parallel blood agglutinins, and in the second series there were 194 positive milk cultures without accompanying blood agglutinins. These results indicate that the presence of agglutinins for *Brucella abortus* in the milk is a better index of milk infection than the presence of blood stream antibodies. The data obtained in the three states were uniform, indicating the widespread distribution of these organisms.

THE MECHANISM OF ANTIBODY ACTION IN RELATION TO PHAGOCYTOSIS AND OTHER SURFACE PHENOMENA
MORTON MCCUTCHEON, BALDWIN LUCKE, STUART MUDD AND MAX M. STRUMIA (BY INVITATION), UNIVERSITY OF PENNSYLVANIA

We have previously reported that whenever acid-fast bacteria were prepared by serum for phagocytosis certain definite changes in the surface properties of the bacteria could be demonstrated. The surface changes correlated with increased phagocytosis are increased cohesion, decreased surface electric potential difference and decreased wettability by oil.

As the result of these studies we were led to the hypothesis that each of the several reactions is determined by the coating of the particle with some serum constituent or constituents. In the present investigation we have obtained evidence

that this constituent is associated with the globulin fraction. Acid-fast bacteria, coated with globulin which has been precipitated from immune serum and then resuspended, behave essentially like those treated with whole immune serum as regards both phagocytosis and other surface reactions. With serum albumin, similar effects were not produced.

The next step was to determine whether globulin plays an equally important role in immunity reactions when antigens other than acid-fast bacteria are used. Rabbits were immunized against soluble antigens: egg albumin, human serum, casein and edestin. Collodion particles coated with one of these antigens were exposed to the corresponding immune serum and its fractions. The results were in every way similar to our previous ones. Particles coated with globulin were prepared for phagocytosis, were agglutinated and had cohesiveness increased and electric charge reduced. We believe, therefore, that these several reactions brought about by specific immune serums depend on the coating of the particle by some substance or substances present in the globulin fraction.

THE HYDROGEN ION CONCENTRATION OF THE INTESTINE J. L. BOLLMAN AND
F. C. MANN, MAYO FOUNDATION

A method has been devised whereby small samples of intestinal contents may be removed at frequent intervals from any portion of the intestine without noticeable disturbance to the animal. Permanent intestinal fistulas were prepared in the following manner. A loop of terminal ileum, about 10 cm. in length, was isolated and the continuity of the intestine maintained by end-to-end anastomosis. The distal end of the isolated loop was then anastomosed end-to-side to the desired portion of the gastro-intestinal tract, and the proximal end of the isolated loop was brought through the abdominal wall and sutured to the skin. In a short time complete healing occurred and the animals appeared entirely normal. Samples of intestinal contents were obtained at frequent intervals during the course of digestion of various meals. The hydrogen ion concentration was determined with the quinhydrone gold electrode system immediately after withdrawal of the samples.

The observations in the first portions of the small intestine showed the greatest changes. In the fasting dog the duodenal contents were usually found to be about p_H 7.6 with occasional variations (in the same animal), seldom as low as p_H 6.2. When milk was fed it began to appear in the duodenum within a few minutes, but there was only a slight diminution of the p_H in the first thirty minutes. After this time, rapid fluctuations in p_H occurred, most determinations being in the region of p_H 5.5, with frequent values of p_H 4.6 and occasional readings of p_H 6.6. About two hours after milk feeding the p_H was more constant and began to rise to about 6.8. Normal fasting values were obtained shortly after this period but wide variations in time occurred, in some animals fasting values were not obtained for twelve hours after feeding, but usually about five hours were required. Following meat feeding the course of events was similar to that described for milk except that the p_H tended to be slightly lower.

The p_H values in the jejunum, 50 cm. from the ligament of Treitz, were more constant. The fasting level varied from p_H 7 to 7.6 and was somewhat influenced by the previous diet. Milk feeding decreased the p_H to about 6.8 for about four hours after feeding, and rapid fluctuations did not occur. After meat feeding the p_H sometimes fell to 6.2 for this same period.

In the ileum, 100 cm. from the ligament of Treitz, changes in the p_H due to digestive processes were not apparent. The fasting p_H was from 7.2 to 7.8 and was somewhat influenced by the previous diet. Occasionally after meat feeding the p_H decreased to 7.

THE INCUBATION PERIOD IN PASSIVE SENSITIZATION WITH HOMOLOGOUS ANTI-SERUM JULIAN H. LEWIS, THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE
AND THE UNIVERSITY OF CHICAGO

The fact that a definite latent period is necessary before the appearance of anaphylactic sensitization after the injection of an immune serum is regarded as

important evidence in support of the cellular theory of anaphylaxis. This latent period is believed to be utilized in fixation of antibodies by the body cells concerned in the anaphylactic reaction and would not be necessary if anaphylactic shock were the result of an interaction of antigen and antibody in the circulating blood as is assumed in the humoral theory of anaphylaxis. Friedberger questioned the necessity of an incubation period in passive anaphylaxis, he claimed that the appearance of an immediate sensitization is prevented as the result of using a foreign sensitizing serum since foreign serums inhibit anaphylactic shock, not only after passive, but also after active sensitization. If the use of a foreign serum is avoided by using an homologous sensitizing serum no inhibition occurs and therefore no incubation period is necessary. Friedberger stated that guinea-pigs sensitized with intravenous injections of guinea-pig immune serum give severe and fatal anaphylactic reactions from three to five minutes after the injection of the sensitizing serum.

The poor response which guinea-pigs give to attempts to produce precipitating serum and the high mortality associated with intensive methods of immunization make it difficult to repeat the experiments of Friedberger. Seibert showed that tuberculous guinea-pigs and those immunized by repeated injections of tuberculin protein have surprisingly high titers of precipitins for the tuberculin protein, reaching in some instances 1:1,000,000. Lewis and Seibert further showed that such serums, in keeping with other precipitating serums, are very active in passively sensitizing guinea-pigs. The ease with which these serums are produced makes possible a thorough testing of Friedberger's observations.

The pooled serum from sixteen guinea-pigs with antituberculin precipitating titers ranging from 1:1,000 to 1:50,000 was titrated for passive sensitizing power. The minimal fatally sensitizing dose given intravenously and with an incubation period of twenty-four hours was 1 cc. A series of guinea-pigs received injections of 2 cc of this serum into the jugular vein, and after periods ranging from three to ten minutes the proper dose of antigen was injected into the opposite jugular vein. These remained entirely unaffected. Another series was sensitized in the same way and received intravenous injections of antigen at various intervals ranging from two to eighteen hours. After two hours there was no reaction, fatal sensitization first appearing four hours after sensitization. As the uterus strip technic is a more sensitive test for anaphylaxis, it was used in virgin female guinea-pigs one, two, three and four hours after an injection of 2 cc of the sensitizing serum. A positive reaction first appeared at the end of two hours, reaching its maximum at the end of four hours. Since it is possible to maintain an isolated uterus strip in an active condition for two hours it was thought possible to sensitize this tissue *in vitro* by exposing it to antiserum for this length of time. A normal uterus suspended in an oxygenated warm bath of Tyrode solution containing 2 cc of antituberculin guinea-pigs' serum (a dilution of 1:250) gave a markedly positive reaction at the end of two hours.

Friedberger's claim, therefore, that an anaphylactic reaction can be obtained without an incubation period when passive sensitization is produced with homologous antiserum, is not corroborated.

THE NATURE OF THE IMMUNITY OF THE SKIN OF THE GUINEA-PIG TO STAPHYLOCOCCUS INFECTION. G. A. PACHECO AND PAUL R. CANNON, THE OTTO S. A. SPRAGUE MEMORIAL INSTITUTE AND THE UNIVERSITY OF CHICAGO

A histologic study of the skin and subcutaneous tissues of the abdominal wall of normal guinea-pigs and of those previously immunized by intracutaneous injections of a staphylococcus vaccine, all infected by the intracutaneous injection of a live virulent culture of *Staphylococcus aureus*, revealed the following general facts. The inflammatory response in the normal animals is characterized mainly by an infiltration of polymorphonuclear leukocytes in moderate numbers, with the result that the infection disseminates and becomes an extensive cellulitis in many instances. In the previously immunized animals, however, the response is more energetic, the exudate contains a large proportion of mononuclear cells and there is increased

activity of the tissue macrophages in the subreticular layer. In addition, immunization leads to a marked thickening of the entire skin, due mainly to increased numbers of fixed tissue phagocytes being either activated or produced, or both. Because of the hyperergic response of the tissue macrophages and of mobile elements as well, the infection is circumscribed and terminated. The conclusions drawn are that the immunity resulting from the intracutaneous vaccination with dead staphylococci is a cellular immunity due to stimulation of the reticulo-endothelial elements of the subcutis, which are not only increased but also react more quickly in phagocytizing and digesting the living staphylococci later injected.

THE EFFECT OF MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS ON THE ANTI-COAGULANT ACTION OF WITTE'S PEPTONE. ELIZABETH CRANSTON (BY INVITATION), O. R. CAILLET (BY INVITATION) AND J. P. SIMONDS, NORTH-WESTERN UNIVERSITY

It was shown in previous experiments that mechanical obstruction of the hepatic veins is accompanied by a marked reduction in the coagulation time of the blood. Witte's peptone in suitable doses decreases or completely inhibits the coagulation of the blood. When peptone is injected intravenously during mechanical constriction of the hepatic veins, (1) there is a delay in the appearance of its anticoagulant action and (2) its anticoagulant effect is less marked. Peptone is believed to reduce the coagulability of the blood through its effect on the liver. Mechanically shutting the liver out of the circulation, however, does not completely prevent this action of peptone.

EFFECTS OF CHOLECYSTECTOMY ON THE BILIARY SYSTEM. CLAIRE HEALEY, ALLAN G. REWBIDGE AND BELA HALPERT, INTRODUCED BY H. GIDEON WELLS, THE OTHO S. A. SPRAGUE MEMORIAL INSTITUTE AND THE UNIVERSITY OF CHICAGO

Opinions differ regarding the effects of the surgical removal of the gallbladder on the rest of the biliary system. In order to gather first-hand information, a preliminary study was made on twelve dogs. The condition of the biliary system was noted at operation, gross and microscopic examination of the gallbladder was made, and the rest of the biliary system was similarly studied after removal from two to sixteen weeks following cholecystectomy. The results thus far obtained suggest the following conclusions: 1. The effects of cholecystectomy depend primarily on the preoperative working condition of the biliary system and on individual anatomic variations regarding the arrangement of the ducts. 2. Cholecystectomy is not followed by dilatation of the intrahepatic biliary ducts. 3. The dilatation of the extrahepatic biliary ducts, if it occurs, is independent of the time elapsing after removal of the gallbladder.

PLASMA p_H IN CANCER. FRITZ BISCHOFF, M. LOUISA LONG (BY INVITATION) AND ELSIE HILL (BY INVITATION), SANTA BARBARA COTTAGE HOSPITAL

The plasma p_H of fifteen normal persons, fifteen patients with cancer who had received no treatment, and ten patients with cancer who had taken radium, x-ray or lead treatment was determined directly by means of the quinhydrone electrode at room temperature. The results were corrected with the oral temperature of the subject for comparison. The normal group showed an average plasma p_H of 7.46 with a minimum value of 7.43 and a maximum value of 7.50. The patients with cancer who had received no treatment showed an average p_H of 7.50, with a minimum value of 7.44 and a maximum value of 7.59. Two thirds of the values for this group were above the highest value obtained in the normal group. The patients with cancer who were under treatment showed an average p_H of 7.52. The observations do not agree with those of Millet who reported no difference between his patients who were normal and those who had cancer.

BLOOD CHEMISTRY STUDIES WITH HENS BEARING ROUS SARCOMA No 1 JOSEPH H ROE, GEORGE WASHINGTON UNIVERSITY

Chemical analysis of the bloods of hens bearing Rous sarcoma no 1 showed no variations from control values in nonprotein nitrogen, uric acid, creatinine, chlorides, cholesterol, serum calcium and inorganic phosphorus, hemoglobin and bilirubin, the analyses being performed at times varying from eighteen days before death to the day of death. A distinct elevation of the blood sugar level was noted. Studies of the blood enzymes showed no variation from control values for the glycogenolytic enzymes of the blood of the sarcoma-bearing hens, but the glycolytic activity of the sarcoma-bearing hens was found to be about twice as great as that of control hens.

THE EFFECT OF SUPRARENAL CORTICAL SUBSTANCE ON THE OVARIES OF CHICKENS AND ON CHICKEN TUMORS CHARLES L. CONNOR, UNIVERSITY OF CALIFORNIA

An emulsion of suprarenal cortex in Ringer's solution, freed as far as possible of epinephrine and excess protein, constantly causes degeneration and atrophy of the ovaries of laying hens when injected subcutaneously or intravenously. The hens stop laying almost immediately, and in many of them aborted eggs are found free in the peritoneal cavity. Eggs and follicles which remain attached to the ovary undergo cystic or hemorrhagic degeneration. When the substance is injected into chickens that have not reached the age of puberty, the ovaries cease growing. A few crowing cocks were injected, in these the testes seemed smaller than in controls and spermatogenesis was absent. The effect seems to be the same as that caused by adrenal cortical tumors in man in whom an excess secretion causes a neutralization of the sex glands.

Because of the known, or suspected, effect of the ovaries on certain tumors in man, chickens that had been inoculated with Rous sarcoma were treated with this substance. It produced contradictory results, as some of the treated animals died before the controls, some died at about the same time, and a few lived longer than might be expected without some sort of treatment.

THE EFFECT OF MUSCULAR WORK ON THE CALORIGENIC ACTION OF THYROXIN C. M. WILHELMJ (BY INVITATION), O. B. BUCKLEY (BY INVITATION) AND W. M. BOOTHBY, THE MAYO CLINIC

The calorogenic action of a single intravenous injection of 10 mg. of thyroxin, in the same dog, when maintained under the same conditions of nutrition, environment, etc., has been previously shown to be constant. In the present series of experiments we studied the influence of daily muscular work of mild, moderate or severe nature on the curve of extra heat production following the injection of 10 mg. of thyroxin. The basal metabolism was determined each morning following the injection of thyroxin, and during the afternoon the animal was given various degrees of muscular work on a motor driven treadmill. In control experiments on the same animal the basal metabolism was likewise determined each morning following the administration of the thyroxin, but during the afternoon the animal was allowed to rest in a small individual metabolism cage under which condition muscular movements were at a minimum. The results show clearly that the extra heat production which follows the injection of thyroxin, in the dog, is not reduced by muscular work, in fact there is a suggestion that the extra heat production may be greater than when the animal is allowed to rest. These observations suggest that muscular work does not increase the rate at which thyroxin is destroyed or eliminated from the body.

THE EFFECT OF SAPOTOXIN AND SODIUM TAUROCHOLATE ON NERVOUS TISSUE ARTHUR WEIL, NORTHWESTERN UNIVERSITY, INTRODUCED BY J. P. SIMONDS

In a previous report it was demonstrated that hemolytic toxins, like saponin cobra venom, streptolysin and sodium taurocholate, act destructively on the myelin sheaths of nerve fibers. Furthermore, it was found that the myelolytic action of

these toxins as well as their toxic effect on rats could be inhibited in the same way as hemolysis by the addition of cholesterol, lecithin, suspensions of red blood cells, brain emulsions, etc. The possible relationship of these phenomena to certain neurologic diseases with primary demyelination was discussed.

In order to overcome the objection that different components of these toxins might produce different biologic action, sapotoxin was isolated from Quillaja saponin in the form of a chemically pure substance. It could be demonstrated that it had the same biologic effects as saponin but was more potent, while the residue of saponin after the elimination of sapotoxin was without effect. According to E. St. Faust, the active principle of cobra venom is closely related to sapotoxin. With sodium taurocholate different histologic pictures are obtained than with sapotoxin. The latter dissolves the myelin sheaths, while the former breaks them up into fine globules which stain dark black with myelin sheath stains. The histologic pictures of cobra venom and streptolysin demyelination resemble that of sapotoxin.

THE LEUKOCYTE CURVE AND ORGAN REACTIONS. E. F. MULLER (BY INVITATION) AND W. F. PETERSEN, UNIVERSITY OF ILLINOIS

The fluctuations of the peripheral leukocyte count, when followed at short intervals over a long period of time, afford an index of the autonomic status of the peripheral tissues, distribution leukopenia being associated with lessened tissue activity, and leukocytosis with increased activity. Many factors may influence this status. Charts were presented to illustrate some of them. Frequently the waves are of increasing amplitude following a single insult. Leukocytic reaction of the internal organs and the possible mechanism of the fluctuation were discussed.

ALTERATION IN THE RESPONSE TO INSULIN DURING EXPERIMENTAL LEUKOCYTOSIS. ISOLDE T. ZECKWER, UNIVERSITY OF PENNSYLVANIA

Each of eight rabbits, under standard conditions, was injected on several occasions with a small convulsive dose of insulin. Then an intense leukocytosis was induced by the intravenous injection of 0.1 Gm. of sodium nucleinate. In five rabbits during the period of leukocytosis, about eighteen hours after injection of the nucleinate, the previously convulsive dose of insulin no longer induced convulsions. These rabbits were allowed to return to normal conditions, when the same dose again caused convulsions. On again inducing leukocytosis by nucleinate, convulsions were again inhibited.

It was necessary to determine if the inhibition of insulin action was due to the leukocytosis or to some other effect of sodium nucleinate. When sodium nucleinate is injected repeatedly, the bone-marrow becomes exhausted of its myeloid elements, so that a rise in circulating leukocytes no longer occurs. When rabbits which previously had shown insulin inhibition during leukocytosis were brought to the stage where sodium nucleinate no longer caused leukocytosis, convulsions again occurred when the same dose of insulin was given, as though no nucleinate had been injected. This would appear to indicate that inhibition of insulin action had occurred because of leukocytosis. The blood sugar just before the insulin was injected was within the normal range in the rabbits so far described.

In three rabbits no inhibition of insulin action occurred during nucleinate leukocytosis, but in these rabbits the blood sugar was low just before the injection of insulin, about eighteen hours after the injection of the nucleinate.

It was found that in the intact rabbit, sodium nucleinate injected intravenously caused an abrupt rise in blood sugar, with a maximum amount at about one hour, followed by a fall to normal or slightly below. The rise did not occur if, some time previous to the injection, one adrenal gland was excised and the opposite splanchnic nerve cut. It was found that insulin inhibition could be induced during nucleinate leukocytosis in two rabbits in which glycogenolysis was prevented by excising one adrenal gland and cutting the opposite splanchnic nerve, if the blood sugar level was within the normal range at the time of the injection of insulin. It was concluded

that when inhibition of insulin action occurred, it was dependent on leukocytosis, not on any effect of nucleinate in mobilizing glycogen

Since insulin is inactivated *in vitro* by the enzymes of leukocytes, it is considered that the insulin inhibition during leukocytosis is probably dependent on the enzymes of the circulating leukocytes. No definite conclusions can be made until more data are obtained, until it is ascertained whether absence of convulsions can be taken as a criterion for inactivation of insulin, and until it is possible to explain those cases in which convulsions were not inhibited during leukocytosis

CONSECUTIVE BLOOD COUNTS ON NORMAL RABBITS OVER LONG PERIODS OF TIME LOUISE PEARCE AND ALBERT E. CASEY (BY INVITATION), THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

Consecutive blood counts on groups of normal rabbits have been carried out over long periods of time for the purpose of obtaining information on the character of the spontaneous variations in the numbers of erythrocytes and of leukocytes and in the hemoglobin content. The observation periods were eight, thirteen, twenty-six, twenty-nine, and thirty-five weeks, respectively, the animal groups comprised four of ten rabbits each and one of five rabbits, the rabbits were young adult males from approximately 6 to 8 months of age, of the common brown or gray type and were representative of those used in other experiments in this laboratory. The examinations were made at weekly intervals, and the supravital neutral red technic was used for the differential white cell counts. The mean values of each weekly group of observations were used in analyzing the results which have been considered primarily from the standpoint of the general trends of cell levels.

It was found that the mean group values of the cells and the hemoglobin content showed certain definite major trends which were of statistical significance. In the first year, both the red cells and the hemoglobin levels became increased, in the second, the red cells were maintained at a fairly constant level but the hemoglobin was increased. In both years, the values for the total white cell count, the neutrophils and the lymphocytes were augmented. The basophils were increased during the first, but were diminished during the second, year. The most prominent feature of the eosinophil results was the abrupt appearance and the comparatively short duration of large numbers of these cells in the peripheral blood, which occurred principally in the spring months. The monocytes showed increased values in the fall and spring months, but on the whole, no generally sustained upward trend of mean values, as was the case with the lymphocytes and neutrophils. The greatest irregularity in the mean values of the various white cells and of the hemoglobin content occurred during the late winter and spring months of both years. The results in the groups examined during 1927-1928 differed from those examined in 1928-1929 in that the general level of mean values of the various cells and of the hemoglobin content tended to be higher during the first year. It was found also that two groups of rabbits examined during the same months usually showed similar and, on the whole, coincident changes in the major trends and even in the more minor fluctuations of mean values.

The value to be attached to these observations is twofold. First, the results furnish information on the character of the spontaneous variations of certain blood constituents which ultimately may be found to have some relationship to environmental conditions. Second, in experimental disease conditions of a subacute or chronic nature, as for example in *Treponema pallidum* infections, the significance of any hemocytologic variation must be interpreted with due regard to the changes that have been demonstrated in normal rabbits over correspondingly long periods of time.

DEVELOPMENT OF THE MYELOBLAST IN CHRONIC MYELOGENOUS LEUKEMIA
RAPHAEL ISAACS, UNIVERSITY OF MICHIGAN

The chromosome number in developing myeloblasts in chronic myelogenous leukemia was 24 in the material studied, in comparison with the usual somatic

number of 48. It is suggested that the reduction in number may have represented an accident in cell division with viable daughter cells which had abnormal growth properties and defective ability to mature. The reduction is similar numerically to that taking place in the developing germ cells, and the clinical results of roentgen therapy in leukemia may be analogous to the artificial parthenogenesis induced in unfertilized germ cells by these agents.

EXPERIMENTAL STUDIES ON MOUSE LEUKEMIA MAURICE N. RICHTER AND E. C. MACDOWELL, COLUMBIA UNIVERSITY, INTRODUCED BY A. M. PAPPENHEIMER

In a previous communication we recorded the existence of a strain of mice in which lymphatic leukemia occurs with great frequency, and reported the successful transmission of leukemia to normal young mice of the same strain. In subsequent experiments it was found that the disease may be transmitted by inoculation of emulsions of various tissues (spleen, liver, lymph node, blood) and that further transfers are possible, apparently indefinitely. In some of the experiments positive results have followed the use of tissues for subsequent transmissions within twenty-four hours after inoculation, but when emulsions prepared from such tissues are used, a longer time is required for the development of leukemia than when the inoculum is prepared from tissues of more advanced cases. The agent responsible for the transmission of leukemia is unknown. Thus far, our experiments indicate that the living cell, or an agent inseparable therefrom is necessary.

Differential counts of living and dead cells in the emulsion (trypan blue method) at the time of inoculation, and experiments with diluted emulsions, indicate that the efficacy of the material, as judged by the time required to cause death from leukemia, is correlated with the number of living cells inoculated. Procedures that deleteriously affect the viability of the cells, such as subjection to heat, or grinding with sand or glass, cause a prolongation of the period of survival which is, roughly, of the same order of magnitude as the increase in the number of dead cells.

Emulsions in which all the cells are killed (by heat, glycerin, or desiccation) or from which the cells have been removed (by filtration or centrifugalization) have been ineffective.

EXPERIMENTAL PRODUCTION OF AN ALEUKEMIC LEUKEMIC CONDITION (A PRELIMINARY REPORT) BERNHARD STEINBERG, TOLEDO, OHIO

An organism with many of the characteristics of *Bacillus proteus* was isolated from the bone-marrow of a boy, aged 15. The patient had marked anemia, leukopenia and a relative lymphocytosis. All the viscera showed a marked lymphoid infiltration. This micro-organism was introduced into the bone-marrow of rabbits, with a reduplication of the blood picture and some of the visceral changes observed in the patient. The organism was recovered in pure culture from the marrow of other bones in the animals given injections. Intravenous and intraperitoneal injections of the bacillus failed to reproduce the disease. Introduction of other micro-organisms—*Staphylococcus aureus* and a hemolytic streptococcus—failed to duplicate the pathologic picture obtained with the bone-marrow organism. The bone-marrow of the patient and of the experimental animals revealed an erythroblastic as well as a mononuclear and lymphoid cell hyperplasia. The total pathologic picture of the patient and of the rabbits was that of so-called aleukemic leukemia.

THE BEHAVIOR OF CERTAIN VITAL DYES INTRODUCED INTO THE CIRCULATION H. P. SMITH, UNIVERSITY OF ROCHESTER

A study was made of the fate of certain acid vital dyes when introduced into the circulation of dogs. These dyes were taken up and stored in granular form in certain phagocytic cells. Evidence showed that the dye is distributed between

plasma and cells in definite ratios. Any disturbance in this equilibrium is followed by passage of dye to or from the cells, with the result that a new equilibrium is established.

THE EFFECT OF FEEDING ON THE RATE OF REMOVAL OF INTRAVENOUSLY INJECTED
PRODIGIOSUS BACILLI FROM THE BLOOD STREAM OF DOGS. J. C. RHIFGOLD,
UNIVERSITY OF ILLINOIS, INTRODUCED BY WILLIAM F. PETERSEN

Bacillus prodigiosus, injected intravenously, disappears at a more rapid rate from the blood stream of fed than of starved dogs. The mechanism of the removal of the organisms is essentially agglutination followed by filtration in the capillary bed (of the splanchnic organs particularly) and their ultimate fate is destruction by the reticulo-endothelial cells. The mechanisms of the increased reticulo-endothelial activity are discussed.

ALKALOSIS OBSERVED IN CASES WITH PERSISTENT HYPERTENSION. EDWARD
MUNTWYLER AND C. T. WAI, WESTERN RESERVE UNIVERSITY, INTRODUCED BY
V. C. MYERS

An acid-base equilibrium study of the plasma has been made on cases with persistent hypertension and with only slight nitrogen retention. A report of three cases is made and at the present time a study is being conducted of two more cases showing similar results. If one assumes 31 mm. as the upper limit for a normal bicarbonate concentration, there was in each case a condition of alkalosis at some period in the observation. The first case showed an uncompensated alkalosis over a period of twenty-two days just preceding death, with the pH varying between 7.54 and 7.56 and the bicarbonate between 34.2 and 36.6 mm. In the second case which did not present as severe an alkalosis as the first, 34.5 mm. was the highest observed bicarbonate concentration. Both cases were characterized by a progressive fall of chloride and total base with a greater decrease of the former than of the latter. Since both of these cases showed periodic vomiting, this may have been the paramount factor in producing the bicarbonate excess, though this cannot be accepted as final as no analyses of the vomitus were made. The third case differed from the first two in that there was no progressive decrease of the chloride and total base concentrations, and further, vomiting was not present. In spite of a normal concentration of chloride there was a bicarbonate concentration of from 28.3 to 32.2 mm. existing over a period of four months. From that time on there was a progressive decrease in bicarbonate to give a terminal uncompensated acidosis. Since the total base in this case remained normal, the undetermined acid concentration (phosphates, sulphates and organic acids) showed a progressive increase.

EXPERIMENTAL PRODUCTION OF INSULIN NEPHROSIS. MILTON G. BOHRD, UNIVER-
SITY OF ILLINOIS, INTRODUCED BY H. R. JAFFE

Normal and pancreatectomized dogs were given large doses of insulin. If the latter lived for more than twenty-four hours, swollen, anemic kidneys were found which were the seat of vacuolar degeneration. Normal dogs died, too, soon after the administration of insulin and revealed similar changes. The condition produced is considered to be an insulin nephrosis, probably due to a disturbance of the water metabolism.

EXPERIMENTAL CANINE DIABETES INSIPIDUS. S. J. MADDOCK, PETER BENT
BRIGHAM HOSPITAL, INTRODUCED BY HARVEY CUSHING

A series of dogs was studied in which diabetes insipidus was produced by closing a silver clip on the stalk of the hypophysis. In one of these animals the polyuria persisted for eighteen months. A complete report of the clinical and

pathologic observations in this dog is presented, together with a brief discussion of the rôle played by the nerve tracts in the tuber cinereum in this syndrome

INTRARENAL ARTERIAL TUBERCULIN INJECTIONS IN NORMAL AND TUBERCULOUS MONKEYS GOATS AND SWINE ESMOND R LONG, CHARLES B HUGGINS AND ARTHUR J VORWALD, UNIVERSITY OF CHICAGO, INTRODUCED BY H GIDEON WELLS

A previous report showed that renal inflammatory changes can be induced by tuberculin injected into the renal arteries of tuberculous swine. In the present report the response in swine and other animals is compared. Tuberculous *Macacus rhesus* monkeys proved to have low sensitiveness to tuberculin. Skin tests led to a soft superficial edema, with little inflammatory change. In two out of three tuberculous monkeys, renal arterial injection of a fine suspension of coagulated tuberculin protein caused a tubular degeneration with many hyaline and waxy casts, but no glomerular or intertubular inflammatory changes, as shown by biopsy a few days after the operation. Autopsy from one to two months later showed complete recovery. Tuberculous goats proved highly skin-sensitive to tuberculin. Of three tuberculous goats one suffered slight tubular degenerative changes on the renal arterial injection of tuberculin protein, one showed acute degenerative changes on the second of two injections, with slight inflammation, and the third showed acute tubular degeneration in the first kidney, injected with many hyaline and waxy casts. A subsequent injection of tuberculin protein into this kidney three months later led to the production of an enormous number of hyaline and waxy casts with no appreciable inflammation and little apparent tubular degeneration. Tuberculous swine were only moderately skin-sensitive to tuberculin. Renal arterial injection in all of three tuberculous swine caused profound fatty degenerative changes in the tubular epithelium, with hyaline and leukocytic casts. In one of these there was marked, and in another moderate, interstitial infiltration with cells of inflammation. Glomerular changes were lacking in all three swine. Biopsy or autopsy a month later showed almost complete recovery. A second renal arterial injection, in the opposite kidney, led abruptly to death in each of two animals so treated. In all animals of each series focal lesions were found which were obviously the result of thrombosis or embolism of small vessels. Two control animals of each type treated in the same manner as the tuberculous animals showed no other changes than those attributed to this focal vascular damage.

THE TEMPERATURE AND ASSOCIATED SERUM CHANGES IN TUBERCULOSIS KNUTE REUTER, UNIVERSITY OF ILLINOIS, INTRODUCED BY WILLIAM F PETERSEN

By means of blood samples taken at frequent intervals during twenty-four hour periods, an effort was made to correlate the alterations in the serum of tuberculous patients with the temperature reaction. Fluctuations of the peripheral leukocyte count, the sugar curve and the enzyme reaction (crepsin) revealed definite relations to the clinical observations.

A QUINHYDRONE-COLLODION ELECTRODE OF SPECIAL APPLICABILITY IN EXPERIMENTAL PATHOLOGY JOHN C BUGHER, UNIVERSITY OF MICHIGAN, INTRODUCED BY CARL V WELLER

A small portion of the fluid to be examined is isolated by the use of a collodion membrane and the contained fluid saturated with quinhydrone. The potential difference developed between a gold-plated platinum wire contained within the small collodion sac and a reference half-cell connected to the outside fluid by a saturated potassium chloride bridge is a function of the hydrogen ion activity of the fluid. The membrane potential is negligible when electrolytes are present in a concentration of one-tenth molar or more. Quinone and hydroquinone, into which quinhydrone dissociates, diffuse through the membrane at practically equal rates, so

that their original ratio is unchanged. The salt effect of the electrode is the same as in other uses of quimhydrone. The electrode is stable in all biologic fluids, including whole blood. It may be incorporated with an electrode vessel forming part of a closed system so that the partial pressures of the contained gases may be maintained at their desired values.

The curve representing the approach to equilibrium is transcendental in character and the equation may be derived directly from the law of diffusion of a solute through a homogeneous phase. The rate at which a given electrode approaches its equilibrium value depends on the thickness of the quimhydrone deposit and on that of the membrane, and is independent of the size of the platinum wire.

The construction of this electrode was illustrated and described.

INFLUENCE OF CLIMATE AND DIET ON GASTRO-INTESTINAL DYSFASIS. LLOYD ARNOLD. UNIVERSITY OF ILLINOIS, INTRODUCED BY WILLIAM F. PETERSEN.

The seasonal variation of the incidence of gastro-intestinal diseases was approached from an experimental angle. There is normally a natural protective mechanism against infection by the oral ingestion of bacteria causing enteric diseases. This bacteria-destroying power is found to be located in the upper half of the small intestine. When an animal is in a state of physiologic equilibrium this segment of the small intestine is almost sterile, and foreign bacteria ingested by mouth or placed directly within the lumen of the upper levels of the enteric tract are destroyed. Body changes brought about by summer temperature, diet and other environmental alterations cause a demonstrable change in the self-disinfecting power of the upper half of the small intestine. Not only do bacteria survive within the lumen, but there is some evidence that permeability of the tract is increased.

This represents a study of the physiologic changes in the host that increase the significance of the microbic life in and around the host.

THE ABSORPTION OF ULTRAVIOLET LIGHT BY BACTERIA. FREDERICK L. GATIS, THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH AND HARVARD UNIVERSITY.

In the ultraviolet region between 220 and 300 millimicrons, different bacteria such as *Staphylococcus aureus* and *Bacillus coli* show characteristic absorption bands so similar as to indicate that they are due to identical chemical groups in the two organisms. Among the chemical entities derived from protoplasm, two groups give absorption bands similar to those for the intact cell. It is evident that one or both of these groups are present in sufficient concentration in the bacterial bodies to dominate in ultraviolet absorption and so to determine their characteristic curves. One of these groups is that of the aromatic amino-acids, built on the benzene ring. The other is made up of certain nuclear derivatives built on the pyrimidine ring. Further study may disclose a means of distinguishing between these two groups in ultraviolet absorption, and of determining which one is primarily involved in such a reaction, for example the bactericidal action of ultraviolet light the incident energy curve for which is approximately reciprocal to the absorption curve for the bacteria in the same region.

THE STRAIGHT AND DIFFUSE PENETRATION OF ULTRAVIOLET LIGHT INTO THE HUMAN SKIN. A. BACHIM (BY INVITATION) AND C. I. RIFE. UNIVERSITY OF ILLINOIS.

By use of various methods, the penetration of visible light and ultraviolet rays from 576 to 236 millimicrons, through various specimens of human skin was determined. The various sources of error were studied or analyzed carefully, and special care was used to imitate the treatment conditions by diverging the experiments. It could be shown that the penetration is governed more by scattering than by

true absorption The distribution of the light through the various layers of skin was determined and the practical limit established that the various parts of the spectrum reach

THE EFFECT OF IRRADIATION BY THE MERCURY VAPOR ARC ON THE ACTIVITY OF PEPSIN AND TRYPSIN DEB B CALVIN, UNIVERSITY OF MISSOURI, INTRODUCED BY A GULICK

THE EFFECTS OF SOLAR IRRADIATION OF LONG VISIBLE AND ULTRAVIOLET WAVELENGTHS RESPECTIVELY, WITH AND WITHOUT SUPPLEMENTARY IRRADIATION OF VARIOUS TYPES, ON THE GROWTH OF CHICKS AND THE DEVELOPMENT OF PARATHYROID GLANDS CHARLES SHFARD, GEORGE M HIGGINS (BY INVITATION) AND WILLIAM I FOSTER (BY INVITATION), THE MAYO FOUNDATION

Under the experimental conditions employed, the grade of stock used and the ration fed in our investigations we believe

1 Constant housing of chicks behind an amber glass filter which transmits only the longer visible wavelengths of sunlight definitely retards growth and development and allows hyperplasia, cystic degeneration and fibrous invasion of the parathyroid glands to occur

2 Constant housing of chicks behind a filter (red-purple corex) which transmits practically only the ultraviolet region 270-400 millimicrons, with a maximal transmission of 20 per cent at 330 millimicrons, rarely permits normalcy in development and growth of chicks as evidenced by weight, and it induces hyperplasia, cystic degeneration and fibrous invasion of the parathyroid glands

3 Normal weights and normal development of parathyroid glands are found in chicks constantly housed behind an amber filter and given daily supplementary irradiation from ten to fifteen minutes with an air-cooled quartz mercury lamp operated at 90 volts and at a distance of 50 cm (ultraviolet irradiation of approximately 575 ergs each second for each square millimeter)

4 Normal calcification of bones (as evidenced microscopically by the Becke method and by the percentage of calcium by weight) and normal weights of chicks occur under several of the experimental conditions imposed relative to quality and quantity of energy with, however, the presence of abnormal parathyroid glands The absence of evidences of rickets or of malnutrition does not argue, therefore for normalcy of parathyroid glands

5 Further evidence is presented, therefore, to support our statement that normal growth and development of chicks and of the parathyroid glands are dependent on both the ultraviolet and the visible portions of solar irradiation, all other factors remaining constant so far as is known

SULPHYDRYL AS A STIMULANT TO CELL DIVISION IN MAMMALS STANLEY P REIMANN, THE LANKENAU HOSPITAL RESEARCH INSTITUTE

Hammett has shown that the sulphydryl group is essential for cell division and that without it, cell proliferation cannot occur The present communication shows that the -SH group attached to such organic radicals as dextrose and cresol increases the rate of cell division in rats and human beings In rats, areas of skin of equal size were removed from each side of the back, dextrose was applied to one side and thiodextrose to the other The wounds to which thiodextrose was applied healed much more rapidly than the others, or normal wounds in these animals

In human subjects the application of thio-compounds also stimulated healing in such conditions as chronic leg ulcers and bed sores Therefore it was concluded that the group -SH, since it also stimulates division in mammals, is a universal stimulant to mitosis

THE RELATION OF INJURY TO PERMEABILITY OF THE CELL TO WATER BAIDUIN
LUCKE AND MORTON McCUTCHION, UNIVERSITY OF PENNSYLVANIA

The unfertilized egg of the sea urchin is an excellent natural osmometer that permits both recognition of injury by decisive criteria and precise measurement of permeability. It has previously been shown that the course of osmosis is satisfactorily described by certain equations by which permeability may be expressed in terms having a definite physical meaning, viz., the number of cubic microns of water entering or leaving the cell per minute, per square micron of cell surface, per atmosphere of difference in osmotic pressure between the interior of the cell and the external medium.

In the present experiments the injurious factors employed were heat and anisotonic solutions. The results were

1 Cells injured by heat (from two to four minutes' exposure to 44 C) remained capable of swelling and shrinking in anisotonic solution.

2 The cells swelled rapidly in hypotonic solutions for a period of several minutes after which they shrank, whereas normal cells continued to swell until equilibrium was attained.

3 When permeability at the first minute was determined in cells exposed to a temperature of 39 C for two, four, eight, twelve and sixteen minutes, and subsequently caused to swell in hypotonic sea-water, a regular series of values was obtained, unheated (control) cells having the lowest permeability and those heated for sixteen minutes the highest.

4 When cells heated for four minutes at 31.0, 36.5, 39.0 and 41.5 C were caused to swell in hypotonic sea-water, the values of permeability were found to vary directly with the temperature.

5 After exposure to a higher temperature (45 C), or prolonged exposure (sixteen minutes) to 44 C, cells were incapable of swelling in hypotonic solutions.

6 When previously normal cells were caused to swell in different hypotonic solutions the values of permeability were the same when calculated for successive minutes (at least during the first several minutes). Increased permeability was found to be an expression of injury.

7 When normal cells previously swollen in hypotonic solutions were returned to isotonic solution and allowed to shrink, the value of permeability was found to be approximately identical for the cells from the different hypotonic solutions. Injured cells, however, had a higher permeability.

8 It was concluded that injury does not at once nor completely destroy the semipermeability of the cell and that the permeability of injured cells to water is greater than that of normal cells.

AN ACTIVATED EXTRACT FOR COAGULATING HEPARIN PLASMA JOSEPH T. KING,
UNIVERSITY OF MINNESOTA, INTRODUCED BY F. H. SCOTT

At present, heparin plasma is widely used in routine planting of tissue cultures. The plasma is coagulated by the addition of an extract of some tissue, usually embryonic tissue.

It has been found possible to increase greatly the power of chick extract to coagulate heparin plasma (rabbit) by adding a small amount of plasma to the extract. After a frail clot has formed, the small amount of fibrin is removed. The extract now is found to have a higher coagulating value. Further, it retains its power over a longer period of time.

The amount of plasma required is small. One part to from 60 to 100 parts extract is used as a routine.

This more powerful extract permits the use of higher concentrations of heparin. Spontaneous coagulation of the plasma in storage is thereby avoided and the operator is assured of prompt clotting when planting.

ALLERGIC, ANAPHYLACTIC AND IMMUNE REACTIONS FOLLOWING INOCULATION OF GUINEA-PIGS WITH HEAT KILLED TUBERCLE BACILLI (READ BY TITLE) ARNOLD BRANCH AND J R CURT (BY INVITATION), HARVARD MEDICAL SCHOOL

The term allergy is employed here to mean that a necrotic reaction occurred after the intracutaneous inoculation of 0.1 cc or 5 per cent old tuberculin, that Long's intratesticular tuberculin reaction was elicited, and that Pfeiffer's intraperitoneal reaction was present. The term anaphylaxis is used when typical lethal or nonlethal shock occurred after the intravenous inoculation of 0.5 cc of old tuberculin. Immunity was considered present when a lymphocytic rather than a monocytic reaction occurs in animals reinfected in the peritoneum or pleura, and when animals inoculated with small doses of living virulent tubercle bacilli outlive controls and show less tuberculosis at death. "Late tuberculin death" signifies that the animals died within twenty-four hours, with subnormal temperature, following a subcutaneous inoculation of 0.5 cc of old tuberculin.

The intraperitoneal, intrapleural or intratesticular inoculation of from 3 to 5 mg, dry weight, of heat-killed (100 C for one-half hour) tubercle bacilli (H 37) in 1 cc of saline solution resulted in allergy, relative immunity and anaphylaxis. Anaphylaxis usually appeared in three weeks and lasted about two months. Allergy usually appeared before anaphylaxis and lasted a longer period. On the other hand, a like dosage of organisms in like dilution, inoculated in two sides intramuscularly, produced anaphylaxis and relative immunity but no allergic reaction. Large doses sometimes produced allergy. Intravenously inoculated animals also showed no allergy, but immunity was not well marked. Late tuberculin death was not elicited in animals inoculated with heat-killed organisms, but in the doses used skin hypersensitivity was not demonstrable in dilutions of old tuberculin above 1:1,000. In infected animals, no matter whether the lesions were localized or disseminated, allergy was readily elicited but anaphylaxis rarely. Skin reactions were often positive to a 1:100,000 dilution of old tuberculin. Late tuberculin death was elicited in all infected animals with one exception, and this animal gave a positive reaction only to a 1:1,000 dilution. The immunity of infected animals was not tested.

Histologic examination of lesions following the various methods of inoculation of heat killed organisms revealed that caseation was always present in allergic animals and absent in nonallergic ones.

These experiments suggest that tuberculous allergy and anaphylaxis are different phenomena, that immunity may occur without allergy and that late tuberculin death occurs only in infected animals that are highly sensitive to intracutaneous inoculation. This is probably a purely quantitative phenomenon, although other possibilities have not been entirely excluded.

Book Reviews

THE PRINCIPLES OF BACTERIOLOGY AND IMMUNITY By W W C TOPLEY, M D, Professor of Bacteriology and Immunology, University of London, Director of the Division of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine, and G S WILSON, M D, Reader in Bacteriology and Immunology in the University of London, London School of Hygiene and Tropical Medicine Price, \$15 Pp 1300, in two volumes, with 242 figures New York William Wood & Company, 1929

This noteworthy book is designed primarily for the student seeking a more thorough training in bacteriology than that offered by the current medical, veterinary or public health curriculum. It is based on the experience of the authors in elementary and advanced teaching and follows the course of study in the London School of Hygiene and Tropical Medicine, with the omission, however, of detailed technical descriptions. There are four parts: general bacteriology, systematic bacteriology, infection and resistance and the application of bacteriology in medicine and hygiene. The first two parts form the first volume, the last two, the second. The pages of the text, the chapters and the figures are numbered consecutively from one volume to the other, both volumes have the same title, but each has its own index and there is no general index. It is, in fact, one book with the index for the first half in the middle. Of course, this is awkward. Even if an index of the first volume seemed desirable, an index covering the whole work at the end of the second volume would have been logical and practical. But this blunder can be remedied easily in the next edition, which surely will be forthcoming before long. The book reflects good standards of workmanship—the page is pleasing, the print clear, the binding substantial and the illustrations, simple as they are in black and white, instructive and helpful.

One may say without qualification that the book is a successful attempt to present adequately the state of knowledge and the trends of advance in the various parts of the broad field of bacteriology and immunity as it relates to infection. The accounts are clear and well balanced, the historical basis in the main is secure, conflicting views are stated with obvious fairness, there is no obscurity in presentation, no undue simplification and no hesitation in stating that no definite conclusion can be drawn from the available evidence when such appears to be the case, as happens to be true frequently (see especially the chapters on hypersensitiveness and on herd infection and herd immunity). At the end of each chapter is a list of references cited in the text which will guide the student in further reading. Naturally many questions might be raised and discussed, for instance: Is the use of the American nomenclature of bacteria, as modified by the authors, warranted? Several surprises, some of them perhaps annoying, await readers especially interested in this question, but the authors are not arbitrary in such matters and always advance reasons that command serious consideration. To some it will seem that the discussion of toxins and antitoxic immunity fails to reach adequate clearness and precision because the use of the word toxin is not limited as exactly as may seem justified from the point of view of the immunologist. Fortunately this is one of few books to give a satisfactory account of the work on the events associated with the formation, course and significance of antibodies in the animal organism. A curious lapse is the complete failure to take any notice of the recent work on the toxigenic action of erysipelas streptococci. While the main purpose of the book is to educate the student to an understanding of bacteriology and its problems, scientific as well as practical, its value as a source of reference and an account of summaries of recent advances should not be overlooked. The student who masters the principles of the book at the same time as he receives commensurate practical training builds a safe foundation for future work.

THE *PENICILLIA* By CHARLES THOM, Principal Mycologist, Bureau of Chemistry and Soils, United States Department of Agriculture, assisted by Margaret B Church, O E May and M A Rames Price, \$10 Pp 644, with 99 illustrations Baltimore William & Wilkins Company, 1930

The first paragraph of the introduction gives a good idea of the subject of this book "The molds of the genus *Penicillium* share with the *Aspergilli* and the *Mucors* a noisome preeminence as weeds They rot our fruit, attack our vegetables and meats, injure our stored grain, spoil our soft drinks and our bottled water, contaminate our pantries and kitchens, and even attack our bodies They infect and at times destroy the usefulness of solutions and moist precipitates, discolor fibers, wood, paper stock, stored paper and sometimes our books In the laboratory they infest and often invalidate every kind of culture operation, bacteriological, mycological, or phanerogamic To offset these activities the chemists have gathered a little return by using them in biochemical investigations and the cheese industry has capitalized their enzymic activity to ripen such cheeses as Camembert and Roquefort Otherwise their possibilities of usefulness remain mostly unknown, but their presence is thrust upon us so frequently that some means of identifying them is very desirable "

The author has been working on the classification of *Penicillia* since 1904, and presents a complete and authoritative work on their history, description, classification and industrial and pathogenic significance, with keys to the identification, bibliography and species, as well as a general index The chapter on pathogenic *Penicillia* is by Margaret B Church and summarizes the recorded reports, most of which are fragmentary and inconclusive The collection of molds of the American Type Culture Collection, with headquarters at the John McCormick Institute for Infectious Diseases, Chicago, is maintained in the Bureau of Plant Industry of the United States Department of Agriculture at Washington, and in it will be found type forms of *Penicillia* described by Thom or received as exchanges This book and the book on *Aspergilli* by Thom and Church (Williams & Wilkins Company, 1926) are great landmarks in the study of molds to which all students of molds must turn for guidance

A MANUAL OF EXTERNAL PARASITES By HENRY ELLSWORTH EWING, United States Bureau of Entomology Price, \$4.50 (by mail, \$4.66) 96 illustrations Springfield, Ill Charles C Thomas, 1929

The main object of this book is to furnish brief sketches of the principal morphologic characters of the external parasites, their life histories and their natural relationships The parasites in question are the mites, the ticks, the biting lice, the sucking lice and the fleas This includes the rat flea concerned in the transmission of plague, the itch mite, the ticks of Rocky Mountain spotted fever, of Texas fever, and of spirochetosis of fowls, the sucking lice of relapsing fever, of trench fever and of typhus fever In preparing the keys for identification, the large collection of parasites recently given to the National Museum by Dr E A Chapin was found of great help This collection is in the charge of the author There is an abundance of good black and white illustrations, and the book contains a large amount of detailed and exact information clearly set forth, with valuable suggestions for control and protection

Books Received

DIE MORPHOLOGIE DER MISSBILDUNGEN DES MENSCHEN UND DER TIERE
Ein Handbuch und Lehrbuch für Morphologen, Physiologen, Praktische Ärzte
und Studierende Unter Mitwirkung Zahlreicher Fachgenossen, Begründet von
Weil Prof Dr Ernest Schwalbe Herausgegeben von Dr Georg B Gruber, o o
Professor der Pathologie an der Universität Göttingen III Teil Die Einzel-
missbildungen XIV Lieferung 3 Abteilung 5-7 Die Entwicklungsstörungen
der Hyphophyse von Prof Dr E J Kraus, Missbildungen der Nebennieren
von Dr W Pagel, Sommerfeld-Osthavelland Die Missbildungen der Epiphyse
des Gehirns von Dr H Wurm, Heidelberg Price, 6 marks Pp 574, with
illustrations Jena, Germany Gustav Fischer, 1929

**THE LIFE OF HERMANN M BIGGS, M D, D Sc, LL D, PHYSICIAN AND STATES-
MAN OF THE PUBLIC HEALTH** By C E A Winslow, Dr PH, Professor of
Public Health, Yale School of Medicine, Member, Health Committee, League
of Nations, Geneva, Member, Public Health Council, State of Connecticut, Past
President, Society of American Bacteriologists and American Public Health
Association Cloth Price, \$5 net Octavo, pp 432, with illustrations Phila-
delphia Lea & Febiger, 1929

THE CHEMICAL ASPECTS OF IMMUNITY By H Gideon Wells, Ph D, M D,
Professor of Pathology, University of Chicago, Director of Medical Research,
The Otho S A Sprague Memorial Institute Second edition, revised and enlarged
American Chemical Society Monograph Series Pp 286 New York The
Chemical Catalog Company, 1929

**DIE FRAGE NACH DEM URSPRUNG DER ENDOMETRIOIDEN METASTASIEN BEIM
GESCHLECHTSREIFEN WEIBE** Von Dr Konrad Heim, Privatdozent für Geburt-
shilfe und Gynäkologie, Oberarzt an der Klinik Price, 8 marks Pp 110 Berlin
S Karger, 1929

**DIET AND THE TEETH AN EXPERIMENTAL STUDY I DENTAL STRUCTURE
IN DOGS** By May Mellanby Medical Research Council, Special Report Series
no 140 Price, 17 shillings, 6 pence Pp 308, with 109 plates London His
Majesty's Stationery Office, 1929

A CLASSIFICATION OF BRIGHT'S DISEASE By Dorothy S Russell Medical
Research Council, Special Report Series, no 142 Price 8 shillings, 6 pence, paper
Pp 248, with 16 plates London His Majesty's Stationery Office, 1929

THE PENICILLIA By Charles Thom, Principal Mycologist, Bureau of Chem-
istry and Soils, U S Department of Agriculture, assisted by Margaret B Church
O E May and M A Raines Price, \$10 Pp 644, with 99 illustrations Baltimore
Williams & Wilkins Company, 1930

RADIUM IN GENERAL PRACTICE By A James Larkin, B S M D, D N B,
Radium Consultant on Staffs of Wesley Memorial, German Evangelical Deaconess,
John B Murphy and Washington Park Community Hospitals, Chicago, and St
Francis Hospital, Evanston, Ill, Instructor in Dermatology (Radium), North-
western University Medical College Price, \$6 Pp 304, with 28 illustrations
New York Paul B Hoeber Inc, 1929

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